THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

OCTOBER, 1961

ORIGINAL ARTICLES

ON THE AGING OF THE HEART; WHY IS IT SO MUCH MORE CONSPICUOUS IN THE BALLISTOCARDIOGRAM THAN IN THE PULSE?*†

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The classic method of assessing cardiac strength is by the pulse, with measurements of blood pressure which allow us to quantitate it; the newer method is by the ballistocardiogram. In general, when the strength of the heart's beating changes acutely, as after exercise, after drugs, or in the beat to beat changes found during arrhythmias, both methods indicate similar changes of cardiac performance.

Unhappily, when these two methods are applied to increase our knowledge of the aging of the heart the results appear to be contrary. Everyone working with the ballistocardiogram agrees that in healthy persons as age advances the record grows smaller (Scarborough *et al.*[3], Starr and Hildreth[9]), the regression of our data for healthy men (Starr and Wood[13]) is given in Fig. 1. But the actuarial data on the pulse pressure, assembled from no less than 250,000 healthy persons by Hunter (Best and Taylor[1]), show clearly that the pulse amplitude of healthy persons increases with age, as seen in Fig. 1. Should one conclude that the heart grows stronger as age advances? The discrepancy between the data provided by pulse and ballisto is a large one and it demands an explanation. Let us consider the problems posed by asking ourselves several questions.

1. Are pulse and ballistocardiogram looking at the same aspect of cardiac function? The physicists write a general equation for the dynamics of things moving which is shown in Fig. 2; everyone is familiar with the under-

*Supported by research grant H-625 (C-8 to 11) from the National Heart Institute, National Institutes of Health, U.S. Public Health Service.

†This work was presented by the senior author at the meeting of the Association of American Physicians held at Atlantic City, May 2, 1961.

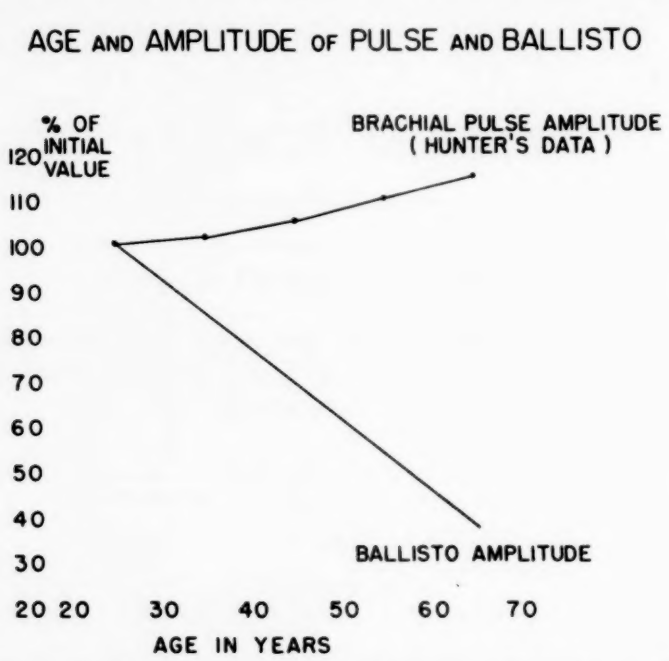

Fig. 1.—Relation of pulse pressure and ballistocardiogram amplitude to age. The difference between the two lines represents the discrepancy mentioned in the title, which it is the aim of this paper to explain.

lying thought from experience with an automobile. The displacement aspect of the movement is that measured by the mileage meter; the velocity aspect is that measured by the speedometer; there is no accelerometer on your car to measure this aspect, but planes have them. As far as the heart is concerned, the cardiac output comes under displacement; the work, as Newton defined it, comes under velocity from which it is computed. Under acceleration come the cardiac forces.

The pulse, a pressure phenomenon and so related to potential energy, is a consequence of the heart's work and so it has been placed under velocity in Fig. 2. The ballisto, as we use it, is a record of forces, and so it has been placed under acceleration in Fig. 2, with certain reservations which may be summarized as follows.

If the heart squirted the blood out of the head end of the body, the ballisto would provide a pure record of cardiac force according to Newton's third law of motion, and the information provided would unquestionably belong under the forces. Actually, the ballisto provides a true record of cardiac force only at the onset of ejection (Starr[4]), in the period before secondary forces generated by the impact of the blood against the aortic arch and pulmonary artery have had time to develop. The latter part of the ballistocardiogram represents the resultant of primary and secondary forces and this complicated play of forces has an effect on the record which resembles, to some degree, a differentiation with a finite time unit representing the difference between the start of each unit ejected and its arrival at the arches (Starr *et al.*[10]).

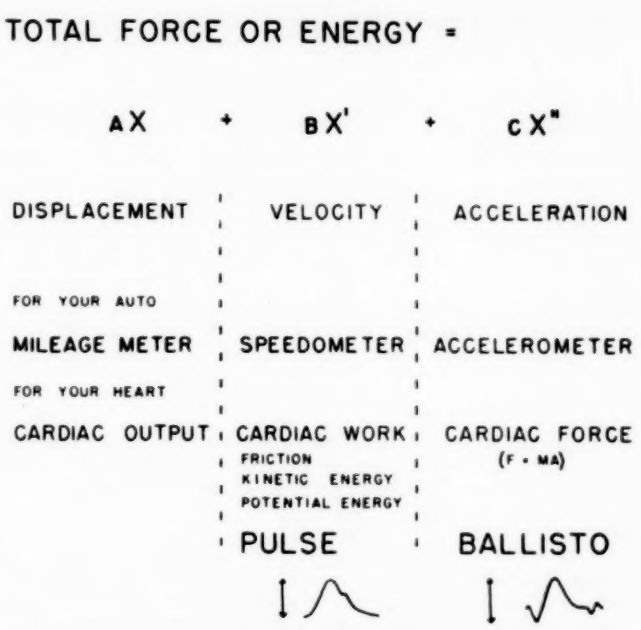

Fig. 2.—The "force" or "energy" equation. The standard differential equation used by the physicists to describe the important aspects of moving objects. The relation of the three aspects of movement represented by the equation, to familiar aspects of the performance of automobiles, and to cardiac performance is also indicated. Pulse and ballisto are placed under the aspects of cardiac performance their amplitude represents, the latter with certain reservations given in the text.

So there is an argument for placing the ballisto farther to the right than its position in Fig. 2 indicates. Despite the uncertainties here, it is clearly evident that pulse and ballistocardiogram, judged by their amplitudes, are not determined by the same aspect of cardiac function and there is no reason to expect that they will give comparable results under all conditions.

The physical theory, given by the equation which heads Fig. 2, further states that these three fundamental aspects of things moving are related to one another mathematically; from frequent readings of your car's speedometer and a watch, one could readily calculate the miles your car traveled. Consequently, different aspects of the pulse relate to different aspects of cardiac performance (Starr[5]). If the pulse amplitude is related to velocity, then the area under the curve is related to displacement and the slope of the curve to acceleration of the ejected blood. If the ballisto amplitude is related to the cardiac forces, the area under it would be related to the velocity components. These relations are indicated in Fig. 3.

So, since there is good reason to believe that the pulse and the ballisto, judged by their amplitudes, are not revealing the same aspect of cardiac performance; the results shown in Fig. 1 permit the interpretation that the heart's forces diminish with age, while the heart's work does not. This is an interesting thought, because, in your car, the acceleration function, your ability to make a jack-rabbit start when the light changes from red to green, is affected by a weakening motor long

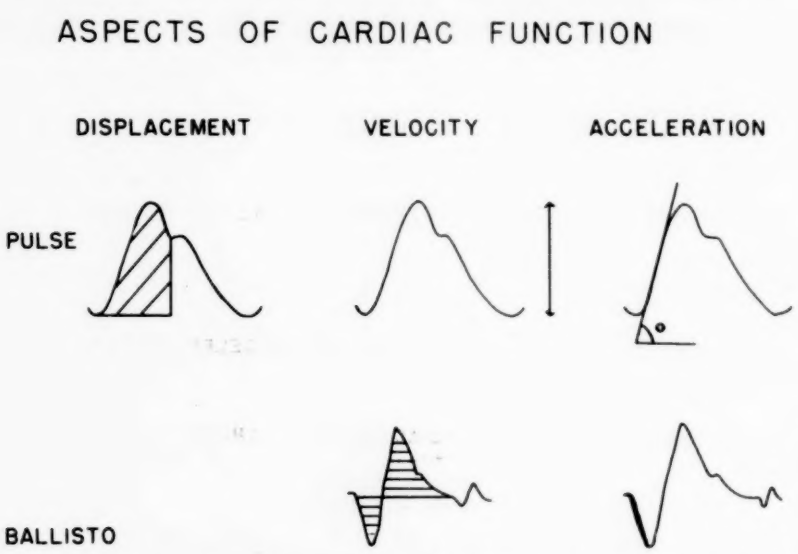

Fig. 3.—To illustrate that different aspects of pulse and ballisto are related to different aspects of cardiac function. Thus pulse amplitude is placed under the velocity aspect of cardiac function, pulse area, under displacement, pulse slope under acceleration. If ballisto amplitude is placed under acceleration, ballisto should be placed under velocity, *etc.* The HI segment, that part of the ballisto record which is the "purest" record of cardiac forces, is represented by a thicker line.

before the velocity aspect, the ability to do 50 m. per h., or the displacement aspect, which gets you home, are impaired.

This intriguing hypothesis can be tested. Let us shift our interest in the pulse from its amplitude to the slope of the advancing wave front, in order to study the cardiac forces from the point of view of the pulse; if our hypothesis is correct, the pulse slope should diminish with age, as does the ballisto. Years ago that fertile source of unplanned experimental data, the clinic, provided hints in this direction. On many subjects the ballistocardiogram and brachial pulse have been recorded simultaneously. One of these subjects, a patient with a bad heart, exhibited some beats that were strong and some that were weak, as judged by the ballisto, although the maximum pulse amplitude of the same beats varied very little (Starr[6]). However, despite the similarity of pulse pressure, close inspection showed that the slope of the advancing pulse wave front ascended steeply when the ballisto was large, and gradually when the ballisto was small. In other words, ballistocardiogram amplitude corresponded, not with pulse amplitude the measure of velocity, but with the magnitude of the 1st derivative of the pulse, the measure of acceleration. This association between ballistocardiogram amplitude and the pulse slope has been seen in many patients, so we have had a strong hint that it is pulse slope rather than pulse amplitude which is more closely related to ballistocardiogram amplitude, as their alignment in Fig. 2 suggests.

In these modern days, instead of making computations, one gets an electrical engineer to design a circuit to do

Fig. 4.—Record of pulse slope at every instant (first derivative of the pulse) under the conventional pulse record taken simultaneously. The straight line to the left of the derivative is its base line, but that to the left of the conventional pulse has no physiological meaning.

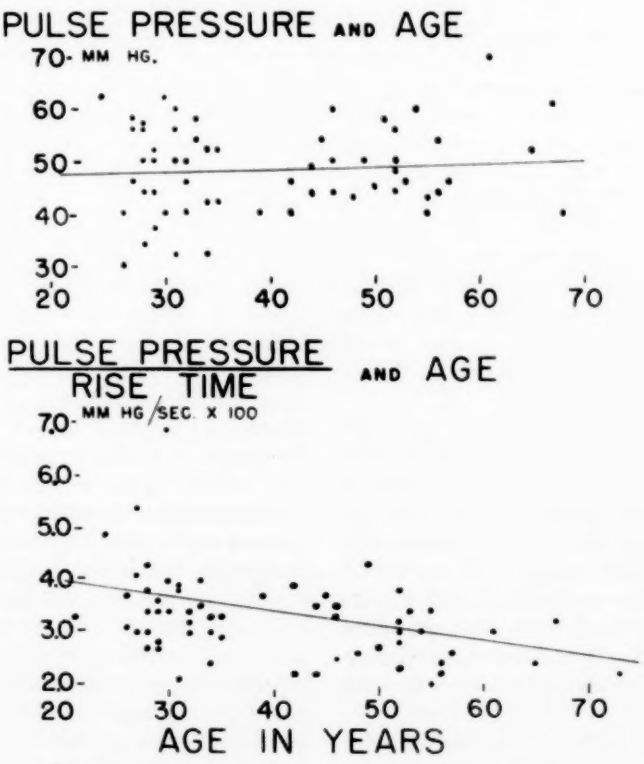

Fig. 5.—Relation between pulse pressure and age; and pulse slope and age in a series of persons, most completely healthy, a few with minor abnormalities not involving the cardiovascular system. The solid lines are the calculated regressions of pulse pressure and of pulse slope on age. Note that the former rises with increasing age, but the latter falls.

them for you, and it proved very simple to secure apparatus which would give continuous record of the slope of the conventional pulse (Starr and Ogawa[11]); such a record, with the conventional pulse record taken simultaneously placed above it for comparison, is shown in Fig. 4.

Such records of the pulse slope, obtained by a transducer on the skin over the brachial artery, have been secured in a large series of patients and healthy persons during the past year. There was difficulty with calibration, but by dividing the pulse pressure secured by the auscultatory method by the duration of the rising pressure, a time value which could be measured very accurately in the pulse derivative records, the average slope of the pulse wave front could be readily estimated.

The results secured in our series of persons without cardiac abnormality are shown in Fig. 5. As in Hunter's actuarial data, the regression of the pulse pressure in our series does not decline with age, but the average slope of the advancing pulse wave front does indeed decline with age as the aging heart lifts its load more slowly. At 65, the average slope is only about ½ that at 25 years.

So, by differentiating the pulse, the diminution of cardiac function with age is made to appear; but we have not proved our hypothesis, for, by integrating the ballisto, that is, concerning ourselves with the area under the curve, the diminution of cardiac function with age does not disappear. We have other things to learn about the discrepancy. So, let us next look for errors in both methods.

2. Could the stiffening of the vessels with age diminish the amplitude of the ballistocardiogram? The genesis of the ballisto has been put on a firm basis by the studies of the Dutch biophysicist Noordergraaf[2]. Many persons have encountered the physical principle concerned when fishing from a boat. The fisherman's hat blows off and lands just behind the boat, but when he moves back to get it, he finds that the boat has moved forward. The basic physical principle is that, when forces arising within an object redistribute its mass, the object, if free to move, moves in space so that the position of its center of mass remains unchanged.

When the heart contracts and blood moves out of it to distend the aortic arch and pulmonary artery, the center of mass of both body and blood moves headward; and the body, if free to move, moves footward, so that the common center of mass remains in the same place. Later in systole, blood accumulates in the peripheral vessels of which those in the lower part of the body are larger, so the common center of mass moves footward in the body, and the body, if free to move, moves headward.

Noordergraaf saw that this movement of the body's center of gravity could be computed from data on the elasticity of the blood vessels and the pressure in them[2]. From the computed curve of the movement of the body's center of gravity at each instant during the cardiac cycle, he calculated, first the velocity of the movement, and then its acceleration. He then multiplied the acceleration at each instant by the weight of the body, to get the forces resulting from the movement of the body's center of mass at each instant; the result is practically identical with normal force ballistocardiograms secured by the best modern instruments. So the genesis of the normal ballisto seems as well understood as anything in physiology, and obviously the elasticity of the vessels, as well as the strength of the heart, is a factor in it. Certainly

if the vessels were completely rigid there would be no movement of the center of mass and no ballistocardiogram; nor could one palpate any pulse, for that matter.

The size of the error due to stiffening vessels as age advances has been carefully studied in cadaver experiments (Starr, Schnabel and Mayock[12]). Noordergraaf's theory requires, but this effect was so small that it was believed to be negligible. The size of the correction is shown in Fig. 6.

In these experiments the expectation that arteriosclerosis itself would cause a significant diminution of ballisto amplitude was never demonstrated, although we had some severely sclerotic

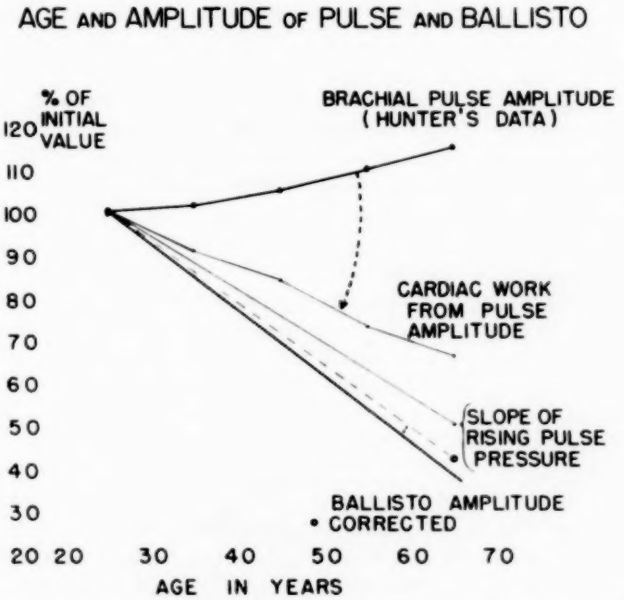

Fig. 6.—Similar to Fig. 1 except that the corrected values have been added. Note the striking effect of the correction of the pulse; the minor effect of the correction of the ballisto (broken line) for the average changes of blood pressure to be expected with aging. The regression of pulse slope on age, also shown in Fig. 5, has also been added.

In these experiments identical systoles could be simulated in cadavers with normal vessels, and in cadavers with advanced arteriosclerosis. Also, in single cadavers, similar systoles could be delivered at the different vascular elasticities which accompanied induced changes of blood pressure. These experiments demonstrated that the changes in vascular elasticity produced by changing the blood pressure from shock to hypertensive levels had a significant effect on the ballisto, as cases (Starr, Schnabel and Mayock[12]). This unexpected result is probably to be attributed to two factors; first, arteriosclerosis is a disease of patchy distribution and, even in advanced cases, a large part of the arterial wall is not involved; and second, in advanced cases both dilatation of the lumen and tortuosity increase the internal area of the vessels. This increase in the area capable of expanding to accommodate blood just received, tends to compensate for the stiffer walls.

Certainly the marked difference in the effect of aging on pulse and ballisto cannot be explained as due to a distortion of the ballistocardiogram by sclerotic vessels as age advances, or to the increased blood pressure which older people show, at the present stage of our knowledge.

3. Is THE PULSE IN ERROR? The most common and familiar source of error in the pulse comes from abnormal obstruction of vessels between the heart and the point of observation. The ballisto has an advantage here, for it is so largely generated by events taking place in the great vessels, that obstruction in the periphery which may blot out the pulse peripheral to it, influences the force ballisto little, if at all. This error, due to abnormal vascular obstruction, will certainly be encountered more frequently in older people, but it causes the pulse to be unduly small in older people, and so the distortion produced is in the wrong direction to explain the discrepancy with the ballisto results in aging.

4. DOES THE PULSE REPRESENT A CONSTANT FRACTION OF THE HEART'S WORK? This seems to be the most pertinent question and cadaver experiments have provided quantitative data which permit an answer. In these old experiments (Starr *et al.*[8]), when systole was simulated in cadavers, the total cardiac work could be calculated with great accuracy. The energy represented by this work goes three ways. Part is dissipated as friction, part appears as flow of blood or kinetic energy, and part as pressure or potential energy; the pulse is related only to the latter.

In the cadaver experiments the work of the simulated systoles (Starr *et al.*[8]), the measure of the cardiac energy available for transfer, could be compared with the amplitude of the pulse, a measure of the maximal gain in potential energy in the circulation during the cardiac cycle. In each cadaver there was a close relation between various magnitudes of cardiac work and the corresponding pulse pressure (Starr[7]). But, when results secured in different cadavers were compared, there was found to be considerable difference in the slopes of the regression lines and in their position with respect to the coordinates; inspection suggested that the slope varies with the subject's age (Starr[7]). One could, therefore, by regression techniques, calculate a correction so that starting from an observation of pulse pressure, one could estimate the total heart's work of any subject with a minimum of error. A multiple regression equation including terms representing the age of the patient and the height of the diastolic pressure, as well as the pulse pressure, proved to contain the items needed to make this correction very effective.

When one applies this calculated correction to Hunter's actuarial data on the pulse amplitude at different ages, the effect, shown in Fig. 6, is very striking. Even though the pulse pressure increases with age in Hunter's data, the cardiac work that it represents diminishes as age advances. So the velocity component of the heart's performance diminishes with age after all.

We have now a satisfactory solution to the problem posed by our title. The discrepancy between the effect of aging on pulse and ballisto has two main causes; 1st, we are not testing the same aspect of cardiodynamic function, and the aspect associated with acceleration of the blood is more effected by age; 2nd, there is a large error in the pulse which masks the effects of age on the heart. To these two major causes we might add the small error in the ballisto due to stiffening vessels.

What is happening in the pulse to

cause this alarming error can be most easily appreciated by consideration of what happens in a simple model such as that shown in Fig. 7. Without doubt the conditions existing in such a model are far simpler than those present in the circulation, but by inspection of Fig. 7 most readers will see immediately the kind of error to which the pulse is subject when one uses it to estimate the strength of the heart, the error to which the data provided by the quantitative experiments point.

The model consists of a syringe with a piece of rubber tubing attached and, to simulate the heart's contraction, a mallet, which, by falling a standard distance, supplies a known amount of energy. In the drawing shown at the top of Fig. 7, the end of the tube is open and resistance to flow is low. This is analagous to the situation found in youth, and, when the mallet falls, outflow is rapid, the friction large because flow is large, and the pressure rise is small. In the bottom of Fig. 7, the end of the tube is shown much closed off; a situation analagous to that caused by the increased peripheral resistance of age. Now the same standard mallet blow produces far less movement of the piston and so less

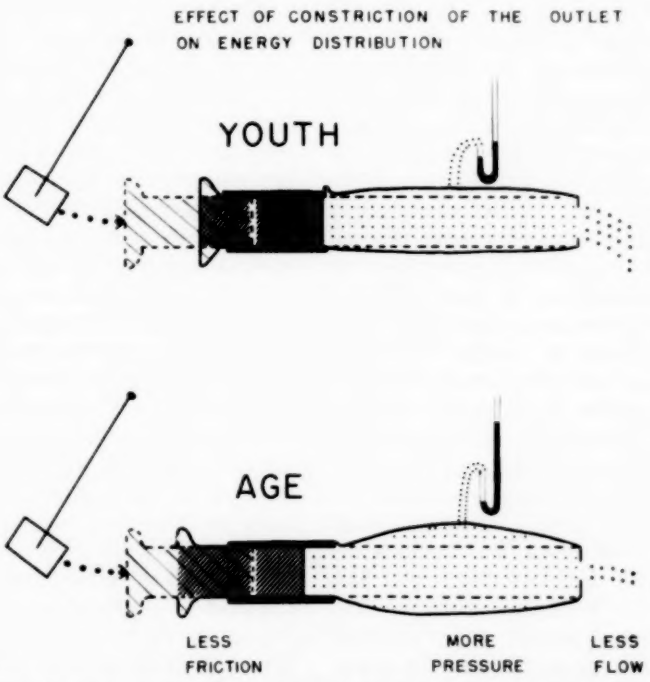

Fig. 7.—Schema to illustrate the redistribution of the energy caused by changes in peripheral resistance. *Above*, the situation of youth, right end of tube widely open, fall of mallet causes large flow and friction, little pressure increase. *Below*, the situation of age with right end of tube much more obstructed. Fall of mallet now causes little flow and friction, the energy going to pressure as the elastic tube is greatly distended. If this is not self evident to the reader he will easily see that, if the outlet were altogether blocked, there would be no outflow so all the energy except that lost in friction, would go to raising the pressure.

friction, and little flow through the constricted end; but the pressure rises high as the rubber is distended. So while the energy put in is the same, the relative distribution of energy in the effect varies greatly, in youth, in the early part of systole, the energy goes chiefly into friction and flow, in age chiefly into pressure. If one were limited to observing the pulse of this system, as we so often are in estimating cardiac strength during life, one would conclude that the energy put in by the heart increased with age. But this is obviously an error. When one judges from the pulse alone, the true state of the heart in age is being masked by the redistribution of the heart's energy.

Unhappily, errors of this type would not be confined to studies of aging. Anyone who has done animal experiments knows that as the heart weakens peripheral vasoconstriction occurs, and, reasoning teleologically, we say that this is for the purpose of maintaining the blood pressure. Vasoconstriction surely has this effect, but it does not seem to have been realized that this physiological response changes the usual relation between pulse pressure and cardiac work and masks the weakening of the heart. So one would not expect observations of the pulse to reveal fully the weakness of the heart until the organ approaches collapse. This error does not seem to have been described previously.

This conception affords a satisfactory explanation for a fact that many have found very puzzling; how was it that the most devastating of the cardiac lesions, cardiac infarction, went unrecognized for so many years by clinicians whose skill and acumen seem to have been every bit as good, and their minds every bit as keen as those of doctors practicing today? Doubtless the idea that the pulse might not be giving firm information about the strength of the heart never occurred to them. Consequently, substernal pains with a normal pulse were attributed to other organs in the area, acute indigestion became a well-known cause of death, and the cardiac origin of the difficulty remained unidentified for many years.

However this may be, the question presented by the title has been answered. If to the corrected version of Hunter's data at 65 years, given in Fig. 7, is added the 50% further reduction justified by the effect of moving our point of interest from pulse amplitude to pulse slope (Fig. 5), and so from the velocity aspects to the acceleration aspects of cardiac performance, the resulting line is very close to the regression of ballistocardiographic amplitude and age. So we have a satisfying quantitative solution, the two independent estimates of the decline of the heart's acceleration function with age are in as good agreement as we have a right to expect, this function declines from its maximum at a rate of about 1½% a year.

We have solved our problem, but at the cost of diminished respect for the classic methods, the pulse and blood pressure, as direct measures of cardiac strength or weakness. Nevertheless, it is consoling to realize that the heart really does weaken with age, even though the pulse does not, for the reverse would be so inconsistent with knowledge of the effect of age on all the other physiological functions of the body, and with the conspicuously diminished ability of older people to lift weights, run races and otherwise disport themselves.

Summary. There is a large error in the old clinical method which seeks to estimate cardiac strength from the pulse. The error is caused by certain physical and physiological properties of the heart and vessels. Of the energy provided by the heart, part is lost as

friction, part manifests itself as energy inherent in moving blood (kinetic energy), and part as pressure (potential energy). The pulse is related only to the latter. When peripheral resistance is low, the heart's energy goes largely to moving the blood and the pressure changes are comparatively small. However, as peripheral resistance increases, a larger and larger part of the heart's work goes immediately to raising pressure and a smaller and smaller part goes immediately to creating blood flow. So the increasing peripheral resistance of aging vessels, and that caused by the peripheral vasoconstriction which seeks to maintain the blood pressure as the heart weakens, both cause a redistribution of the heart's work so that a larger proportion goes into the initial increase of potential energy which we detect as the pulse, and this change masks the weakness of the heart.

This conception explains why the pulse amplitude fails to show the decline of cardiac strength as age advances, and why clinicians of the era which trusted the pulse to reveal cardiac weakness, failed to identify the most destructive of cardiac lesions, cardiac infarction, during life.

When one corrects for this redistribution of energy as age advances and shifts one's attention from pulse amplitude to the slope of the advancing wave front, the aspect of cardiac function measured is found to decline with age at a rate of about 1½% a year, a rate in excellent agreement with that measured by the declining amplitude of ballistocardiograms as age advances.

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SUMMARIO IN INTERLINGUA

Le Invetulation del Corde: Proque Es Illo Tanto Plus Conspicue in le Ballistocardiogramma Que in le Pulso?

Il existe un considerabile error in le ancian methodo clinic que tenta determinar le fortia cardiac a base del pulso. Le error es causate per certe proprietates physic e physiologic del corde e del vasos. Un parte del energia providite per le corde es perdite como friction, un parte se manifesta in le energia inherente in sanguine in movimento (energia cinetic), e un parte appare como pression (energia potential). Le pulso es relationate solmente con iste ultime. Quando le resistentia peripheric es basse, le energia del corde se utilisa in grande parte in mover le sanguine, e le alterationes de pression es comparativemente micre.

Tamen, quando le resistentia peripheric monta, un semper crescente parte del travalio del corde se utilisa immediatemente in augmentar le pression e un semper decrescente parte se utilisa immediatemente in mantener le fluxo del sanguine. Assi le crescente resistentia peripheric de vasos invetulante e illo causate per le vasoconstriction peripheric que visa a mantener le pression del sanguine durante que le corde deveni plus debile, ambe istos causa un redistribution del travalio del corde de maniera que un plus grande proportion es usate in le augmento initial del energia potential que nos detege in le forma del pulso, e iste alteration masca le debilitate del corde.

Iste conception explica proque le amplitude del pulso non monstra le declino del fortia cardiac que occurre con le avantiamento del etate e proque le medicos del era que habeva fide in le pulso como indice de debilitates cardiac non succedeva a identificar le plus destructive del lesiones cardiac, i.e. infarcimento cardiac, durante le vita del patientes.

Si on introduce un correction contra iste redistribution del energia con le avantiamento del etate e torna su attention ab le amplitude del pulso ad le pendentia del avantiante fronte de unda, il es trovate que le aspecto de function cardiac mesurate declina con le etate in un mesura de circa 1½% per anno. Iste mesura se trova in excellente concordantia con le mesura reflectite in le declino de amplitude del ballistocardiogramma in le curso del avantiamento del etate.

(See page 415 for original article)

SUMMARIO IN INTERLINGUA

Mucormycosis

Mucormycosis—un extraordinarimente acute e usualmente mortal infection per fungos del ordine Mucorales—pote occurrer in patientes con diabete o leucemia. Nos opina que antibioticos in le caso de diabeticos e antimetabolitos in le caso de leucemicos age como "catalystas" effectuante un infection per ille usualmente innocente saprophytos.

Duo casos de mucormycosis cranial es reportate. Le indicios, que permitte un precoce diagnose clinic, es describite. Le prime del presente casos occurreva in un diabetico non stabilisate sed etiam non acidotic qui habeva essite sub tractamento con drogas anti tuberculosis. Le secunde caso se disveloppava in un diabetico in acidosis a qui chloramphenicol habeva essite administrate como tractamento de un infection del vias urinari.

Le restablimento del prime patiente sequeva un intervention chirurgic e non pote esser attribuite a ulle medication. Le restablimento del secunde patiente es attribuite al tractamento con amphotericina B e a un intervention chirurgic.

AMINO-ACIDURIA IN SALICYLATE INTOXICATION

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In the past decade, amino-aciduria was reported in lead (Wilson, Thompson and Dent[21]), uranium (Rothstein and Berke[15]), cadmium (Clarkson and Kench[5]), lysol (Spencer and Franglen[16]), and Vitamin D (Van Creveld[19]) poisoning and was produced experimentally with maleic acid (Harrison and Harrison[8]). This paper reports the finding of amino-aciduria in children who ingested excessive amounts of salicylate.

Material and Methods. Five patients on the Pediatric Service of Walter Reed General Hospital were observed for salicylate intoxication and studied for the presence of amino-aciduria. Eight 24-hour urine specimens were obtained for controls from patients awaiting elective surgical procedures and children of physicians. Blood salicylate levels were obtained and 24-hour urine collections were begun immediately upon admission to the hospital for the study group patients. Blood and urinary salicylates were determined by Kazyak's method[9]. Individual amino acid standards were made by Levy and Chung's[11] procedure and color development of the urinary chromatographs made with Moffat[12] and Rosen[14] stains. Chromatography stain densities were determined with a Spinco Analytrol. Alpha-amino nitrogen was determined by the copper technique of Kekki[10].

Results. The data for these patients are presented in Table 1. Patients are listed in the order of decreasing amounts of α-amino nitrogen in their urines. Blood salicylate levels on admission and approximate amounts ingested are included for information. A close relationship is noted between the amount of α-amino nitrogen and salicylates in the urine. The addition of salicylate to control urines, however, did not increase the amounts of α-amino nitrogen measured. Patient 5 received gastric lavage within 15 minutes after ingestion of methyl salicylate. His values are included for comparison only, since his α-amino nitrogen excretion values fall into the control range of 1.9 to 4.5 mg. per kg. per 24 hours. These contrast with values in the range of 10.3 to 25.0 mg. per kg. per 24 hours for the remaining patients in the study group. Follow-up studies revealed a return to normal levels of α-amino nitrogen excretion at a later date in all patients which suggests that the disturbance is transient.

Urinary amino-acid chromatography patterns of a normal control and a patient with salicylate intoxication are compared in Fig. 1. A prominent increase in cystine, arginine, histidine, methionine, asparagine, lysine, glycine, glutamic acid, alanine, proline, tyrosine, valine and leucine is demonstrated. Similar excretion patterns were seen in all patients with elevated blood salicylate.

TABLE 1.—AMINO-ACIDURIA IN SALICYLATE INTOXICATION

Pt.	*Age*	*Weight in kg.*	*Estimated amount of salicylate ingested in gm.*	*Admission blood salicylate level in mg. per 100 ml.*	*Acute total 24-hour urine salicylate in mg.*	*Acute total 24-hour urine α-amino nitrogen in mg.*	*Recovery total 24-hour urine α-amino nitrogen in mg.*
1	3	13.6	Unknown	53.2	368.2	340.1	40.6
2	2½	14.5	4.000	59.2	438.4	244.0	
3	3	19.2	2.220	41.0	318.8	197.2	86.1
4	2½	15.0	3.840	46.1	715.0	162.4	34.3
5	3	15.0	3.000	4.2	14.3	35.4	
							α-amino nitrogen excretion in mg./kg./24 hr.
					Study patients (excluding No. 5)		Range 10.3–25.0 Mean 15.7
					Eight control patients		Range 1.9–4.5 Mean 3.1

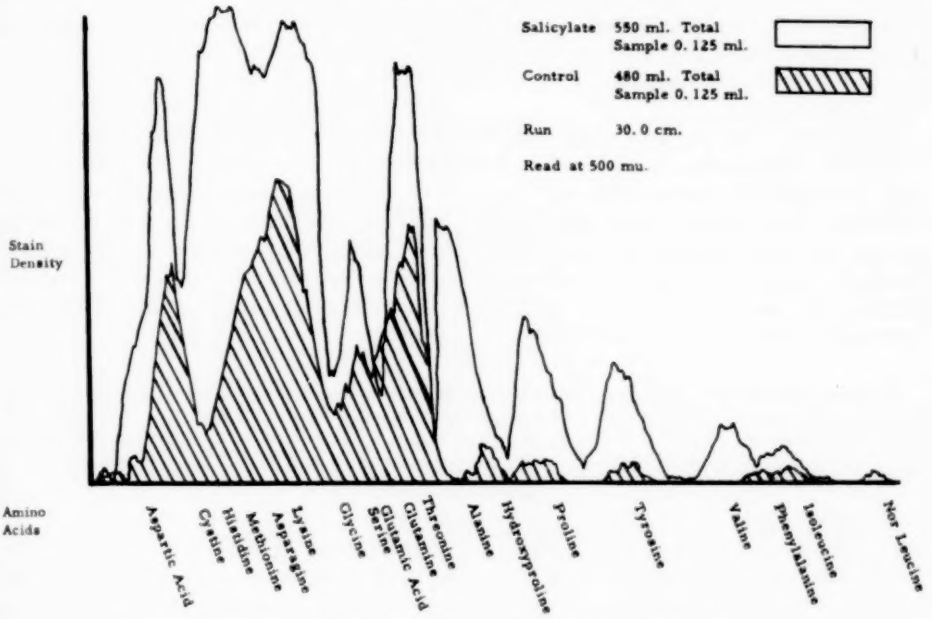

Fig. 1.—Urinary amino acid chromatography in a control and a patient with salicylate intoxication.

Discussion. The amino-aciduria observed in the patients of this study grossly exceeds values observed in children either on high dosages of steroids or following prolonged surgical procedures (Andrews[1], Sutton[18]). Therefore, the mechanism of such stress producing amino-aciduria is not supported.

A toxic action upon the proximal renal tubular enzymes or transport systems, or both, is felt to result in the generalized amino-aciduria observed in other poisonings (Chisolm *et al.*[3], Ghadimi and Shwachman[6]). However, the amino acid excretion patterns of our patients are different. They strongly resemble the "overflow" amino-aciduria of hepatic injury (Chisolm and Harrison[4], Walshe[20]) because the sulfur-containing amino acids are markedly increased. Liver injury following salicylate intoxication has been documented throughout the literature (Gross and Greenberg[7]).

Recent investigation has shown that salicylates are capable of uncoupling oxidative phosphorylation (Brody[2], Sproull[17]). This action may explain the hyperglycemia and ketosis observed in salicylism (Winters *et al.*[22]). Also, the incorporation of amino acids into protein depends upon aerobically formed high energy phosphate (Quastel and Bickis[13]). We suggest that the amino-aciduria may also be the result of the uncoupling action of salicylates upon oxidative phosphorylation. The changes in carbohydrate, lipid and amino acid utilization tend to support the *in vitro* observations (Brody[2], Sproull[17]) of interference with normal energy metabolism resulting from the ability of salicylate to block the production of high energy phosphate.

Serum α-amino nitrogen levels were not measured simultaneously with urine determinations. Further studies are, therefore, indicated to rule out a

renal tubular mechanism and to elucidate more completely the mechanism of this newly recognized cause of amino-aciduria.

Summary. Five patients observed for salicylate intoxication were studied for the presence of amino-aciduria. In 4 patients with blood salicylate levels above the usual therapeutic range, generalized amino-aciduria was observed. Follow-up studies on these patients revealed a return to normal values.

Amino acid chromatography patterns closely resembled those reported in hepatic injury in that the sulfur-containing amino acids were markedly increased. This observation would support a renal "over-flow" mechanism for the amino-aciduria. The recently described ability of salicylates to block production of high energy phosphate may be responsible for a failure of incorporation of excess amino acids into protein.

ACKNOWLEDGMENTS: The authors wish to acknowledge the technical assistance of Dr. Larissa de Baare and Pfc. Richard J. Van Apeldoorn, and the assistance of Major Milton Rubini and Major Edward Tomsovic of the Walter Reed Army Medical Center in preparing this paper.

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(Interlingua on page 435)

MUCORMYCOSIS

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In 1885, Arnold Paltauf[8] ended his classic paper on mucormycosis thus:

"The observations described here are of limited importance for practical medicine—because of the rarity of the disease and because there is no treatment for it. Nevertheless, they enrich our knowledge; and no experience or extension of our knowledge of natural processes is so insignificant that it is not worth knowing and recognizing."

Paltauf's belief that his recorded observations of "natural processes" might prove to be significant some day, despite the immediate unimportance of mucormycosis, was accurate.

Mucormycosis, an infection caused by fungi of the order Mucorales, is, after a hiatus of over a half century, being recognized with increasing frequency. Paltauf has been credited with being the first to describe a valid case of mucormycosis in man, but he referred to 2 cases reported by Fürbringer[3] and another possible case (Cohnheim[2]) as being the only "hitherto recognized and valid cases of mucormycosis vegetation in man" (these cases involved lungs only). McBride, Corson and Dammin[5], who in 1960 reported on 2 cases discovered at necropsy, stated that "57 acceptable cases" (including their own) had been reported in the English literature (their figure should be 56 since they included Paltauf's case); the first cases were reported in 1943.

In the past 3 years we have had 2 patients with mucormycosis on the Medical Service of this Army Hospital; both recovered. The second patient, a rare instance of the diagnosis of mucormycosis *preceding* any histologic and mycologic studies, received amphotericin B. We know of only one other patient (Prout and Goddard[9]) successfully treated with this antifungal agent, although in 1958 Osswald and Seeliger[7] published an excellent paper on experimentally infected mice successfully treated with this drug.

One purpose of this paper is to describe in detail the clinical manifestations which should lead to more frequent antemortem diagnoses. The other purposes are to add 2 cases to the literature and to report on recovery attributed to the use of amphotericin B.

Case Reports. CASE 1. The first patient was a 50-year-old man. Pancreatitis had been diagnosed in 1955, diabetes and tuberculosis in 1956; he had been taking 300 mg. of isoniazid daily and receiving 1 gm. of strepto-

mycin twice weekly for a year and a half preceding his admission. He ceased taking NPH insulin in March, 1957, because urinalyses no longer disclosed glycosuria.

On 9 September 1957, he began to have pain in the right malar area. On 13 September, he noticed increased swelling and redness but decreased sensation of the right side of his face; 2 days later his right eye became prominent. Despite increasing swelling and onset of diplopia, pain did not increase. No fever or chills were experienced.

He entered the Martin Army Hospital (Fort Benning, Georgia) on the afternoon of 16 September 1957, the eighth day of illness.

On admission, his temperature was normal (but was 99.6° on the next day) and his pulse rate was 110. He did not appear to be in acute distress. His right cheek was moderately swollen, hot, hard and without any sensation. Right facial muscles were weak. His right eye protruded and was immobile, but he could see normally when it was in the primary position. The right half of his hard palate was gray and was sharply demarcated at the midline. Ophthalmoscopy revealed no abnormalities. Size of pupils was equal and normal; they reacted normally. Corneal reflexes were present.

By 19 September, proptosis of the right eye had increased, and he had pain in right eye and frontal area. The neurologic consultant stated that the third, fourth, fifth, sixth and seventh right cranial nerves were functionless, and that absent gag reflex and paresis of the right side of his palate implied involvement of the right ninth and tenth cranial nerves. The right half of his hard palate was now dark gray. Fundal examination still failed to reveal venous distention or other abnormalities. On the next day, malar swelling reached its height; his temperature ascended to 102° and pulse rate to 118.

Investigations. Leukocyte count, which was 13,250 with 87% neutrophils on admission, ascended to 15,650 on 19 September, then subsided slowly.

A lumbar spinal tap, on 19 September, disclosed normal pressure. No cells were seen; smears and cultures did not reveal bacteria (no cultures for fungi were ordered). Protein was 48 mg. per 100 ml. Glucose content was not determined. Culture of aspirate from right antrum, on 27 September, yielded "*Escherichia coli*, resistant to all antibiotics." No cultures for fungi were ordered.

The lung roentgenogram, which revealed "infiltrate" and nodular densities in the right apex and calcification of the right hilum, was similar to those taken during 1957 to 1960 and was compatible with tuberculosis. Roentgenography of the skull, on 19 September, revealed homogeneous clouding of the right maxillary, frontal and ethmoid sinuses. The roentgenologist stated: "films do not definitely indicate bone erosion;" yet areas of floor and medial wall of right antrum were "under suspicion as to bone erosion." He concluded that the differential was between "sinusitis and involvement of the right sinuses by neoplasm."

Fasting blood glucose level (on 18 September) was 345 mg. per 100 ml. Carbon dioxide combining power was not determined. Initial urinalysis, on 17 September, disclosed "4 plus" glycosuria, but no ketonuria, a trace of albumin and occasional hyaline and granular casts; a second urinalysis disclosed "occasional WBC and RBC." Thereafter, urinalyses showed no abnormalities except for glycosuria and infrequent ketonuria. After 2 weeks, glycosuria was infrequent and ketonuria was absent.

Surgery. On 3 October 1957 an antrotomy was performed. The anterior wall of the antrum was extremely soft. A mass of gray necrotic tissue was found. Necrotic portions of the hard palate, antrum and the turbinates were removed by forceps. Specimens for biopsy were taken from the right antrum and palate.

On 10 October, the antrum and adjacent structures were resected. Necrosis was found to extend to the sphenoid sinus and to the cribriform plate. After removal of all necrotic tissue, only the infraorbital rim of the right antrum remained. The cavity was irrigated daily and packed with gauze soaked in a carbowax preparation of papain (a proteolytic enzyme used to remove the necrotic tissue close to large blood vessels). On 12 November, a right tarsorrhaphy was done because the right cornea had begun to ulcerate. Use of gauze packs ceased on 26 November and irrigations on 24 December 1957.

Medical Treatment and Course. During the first 10 days, daily dose of insulin was 40 to 50 units, then it was gradually decreased; and in January, 1958, insulin requirement varied between none and 10 units daily. Streptomycin and isoniazid were continued, the former in a dose of 1 gm. semi-weekly, the latter in a dose of 300 mg. daily. Because the initial diagnosis was acute cellulitis, presumably due to a bacterium, administration of penicillin (1,200,000 units daily) was begun on 19 September. On 23 September, chloramphenicol was added; on that day, before it could be effectual, cellulitis and

fever began to recede. His temperature ranged from 99 to 101° (except for an increase to 102° on each of the days of operation) until 17 October 1957. Thereafter it was normal. Penicillin and chloramphenicol were discontinued on 1 and 17 October respectively.

On 17 October 1957, more than one month after the first symptom, the pathologist's report was received. It stated that microscopic examination of osseous and soft tissue obtained from the right antrum and the palate had revealed extensive necrosis, bone destruction, capillary proliferation and inflammatory changes associated with many clusters of very large hyphae, up to 200 mu. in length. The hyphae were broad, branching, nonseptate and characteristic of Rhizopus. As soon as this report was received, antibacterial treatment was stopped. Nystatin was then used to irrigate the antrum and to impregnate the antral packing.

Potassium iodide (three 400 mg. capsules daily) was begun on 18 October, although he had already improved markedly. Improvement continued.

At the time of discharge (17 January 1958), proptosis and signs of cellulitis were absent and his weight (which had decreased from 147 lb. on admission to 113 lb.) was 132 lb. He was re-examined 3 years later. He weighed 148 lb.; he had a satisfactory oral prosthesis occluding the bone defects; his left eye was still occluded by the tarsorrhaphy; and his left malar area was moderately depressed.

CASE 2. This patient, a 33-year-old American Indian, was semi-comatose when he was admitted to Martin Army Hospital, on 9 October 1960. Examination on admission revealed obesity (225 pounds), rapid breathing (36 per min.) and a semi-comatose state. Except for dry mouth, there were no other abnormalities. After he regained consciousness, he denied personal and family history or symptoms of diabetes mellitus. During hospitalization earlier in 1960, for evaluation of mild hypertension, urinalyses revealed no glycosuria.

Initial laboratory tests disclosed "4 plus" glycosuria, strongly positive ketonuria and 10 to 12 red blood cells in each high power field. Blood glucose was 410 mg. per 100 ml. Serum acetone test was strongly positive in a 1:2 dilution, moderately positive in 1:4 dilution. Blood CO_2 was 10.6 mEq. per L., urea nitrogen was 45 mg. per 100 ml.

He was treated for diabetic acidosis and 10 hours after admission he was much improved; acidosis was no longer a problem, but hyperglycemia, oliguria and glycosuria were still present. Blood urea nitrogen rose during the ensuing 3 days, to 83.6 mg. per 100 ml., but fell to 35 mg. on 15 October.

On 13 October 1960, he began to receive chloramphenicol because of urinary tract infection. On the morning of 17 October, he complained of a left maxillary "toothache" and left temporal headache and was seen in the dental and ENT clinics. A small yellow area, about 0.5 cm. in diameter, seen on the anterior part of the middle turbinate, was believed to be a crust of dried serum. No edema, redness, purulent discharge or any other abnormality was present.

On 20 October, chloramphenicol was replaced with procaine penicillin and streptomycin because the entire left side of the face had become swollen and the left eye protruded. Roentgen-ray films of the sinuses revealed indications of bilateral maxillary sinusitis, left more than right, and left ethmoid sinusitis.

Aspiration of the left maxillary sinus yielded no pus; irrigation resulted in a return of clear liquid.

On 21 October, after learning that cultures of nasal secretions and aspirate from the left maxillary sinus, obtained on 20 October, had revealed *Pseudomonas aeruginosa*, penicillin was replaced by 50 mg. of polymyxin B (intramuscularly every 6 hours).

On 21 October, the marked similarity to Case 1 and the detection of barely discernible, yet sharply demarcated grayness of the left side of the palate led to our making a clinical diagnosis of mucormycosis. The infection with *Ps. aeruginosa* was believed to be predisposing or concomitant. We then sought to obtain specimens for biopsy, to confirm the diagnosis.

On 22 October, specimens of mucosa and bone were taken from the left maxillary and ethmoid sinuses. During the operation, we observed almost complete absence of bleeding and abnormally soft consistency of bone of the palate and maxillary sinus, indicative of necrosis, and attributable to widespread thrombosis. These observations, the dusky-red, swollen appearance of sinus mucosa and the absence of need for local anesthesia strengthened the probability of mucormycosis. Later on the day of operation, we began antimicrobial therapy, directed at fungi and Pseudomonas: per-oral saturated solution of potassium iodide (1 gm. every 4 hours), polymyxin B (50 mg., intramuscularly every 6 hours) and sinus irrigations with nystatin and Tryptar, a proteolytic enzyme. On 23 October, the left hard palate was dark gray; on the next day this area was black. Swelling of the face was unchanged.

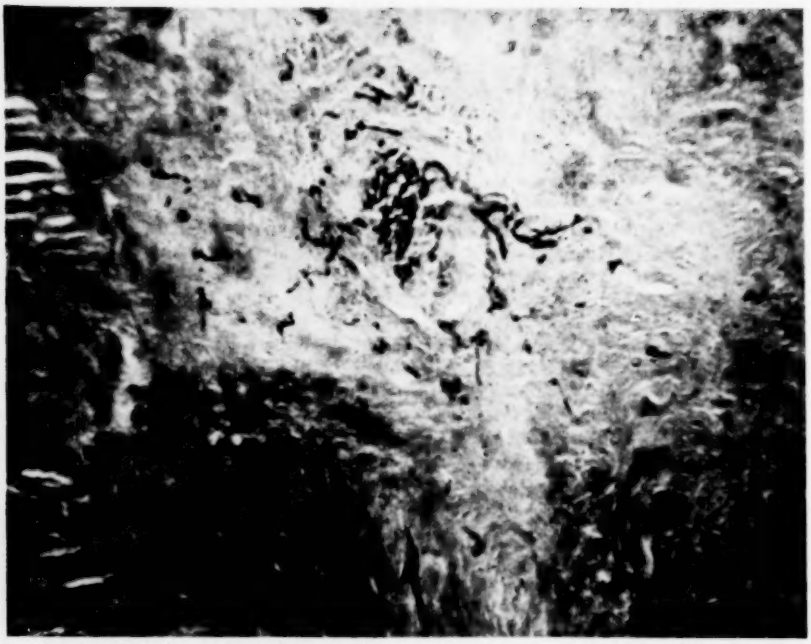

Fig. 1.—Tissue from left ethmoid sinus showing thrombosis and necrosis of a medium sized vessel. Note numerous hyphae (black, thread-like objects) in the thrombus, extending through the vessel wall into the surrounding tissue. Minimal inflammatory reaction is present. Iron hematoxylin; × 100.

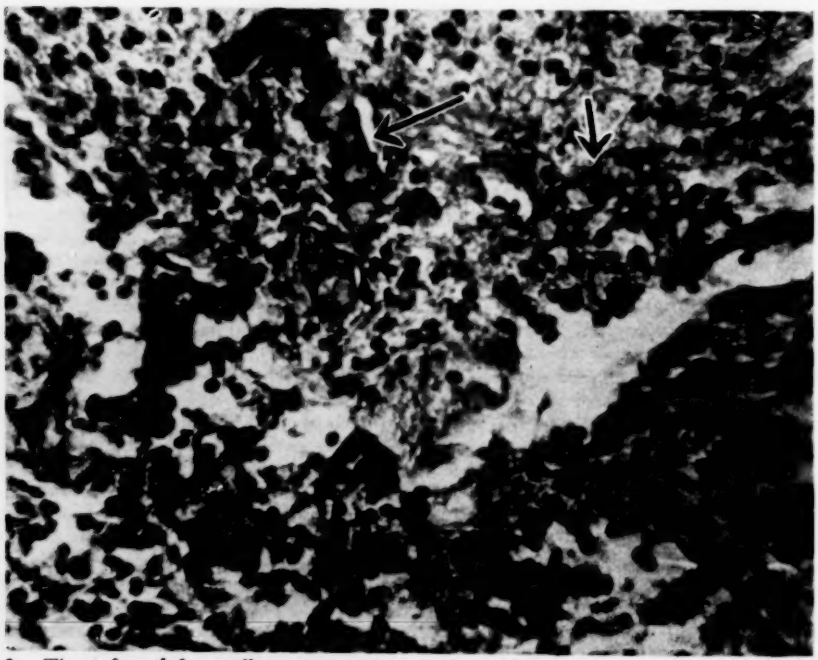

Fig. 2.—Tissue from left maxillary sinus. Note the large size and the nonseptate and branching character of the fungus (arrows). Iron hematoxylin; × 430.

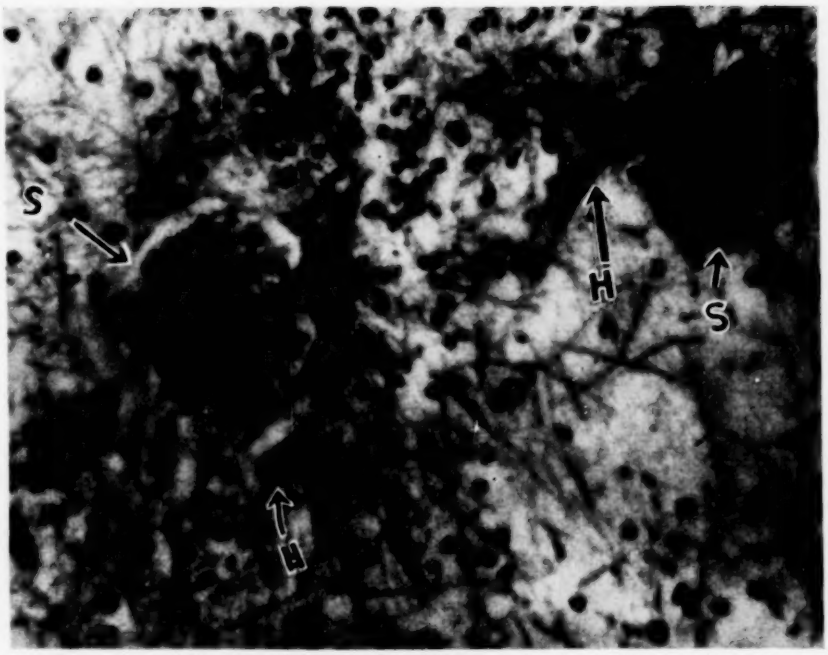

Fig. 3.—Tissue from left ethmoid sinus. In addition to hyphae (H) mycelia and sporangia (S) containing spores are shown. Scattered spores and inflammatory cells are present. Iron hematoxylin; × 430.

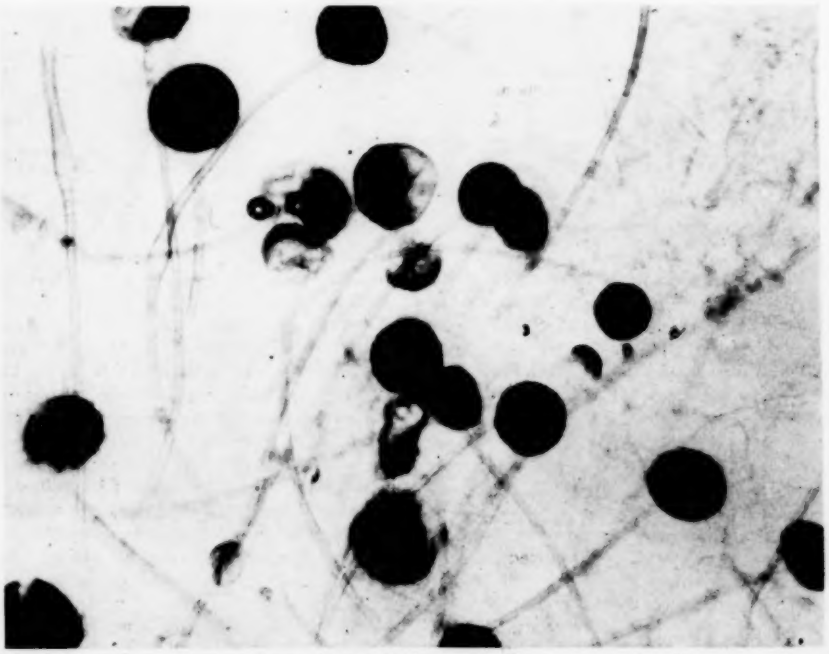

Fig. 4.—Wet mount, from culture obtained from maxillary sinus, showing spore-containing sporangia attached to sporangiophores; × 430.

On 24 October the pathologist stated that stained sections of tissue revealed the presence of a fungus believed to be of the genus Rhizopus (later identified as *Rhizopus nigricans;* culture of tissue also yielded *R. nigricans*). On 24 October, treatment was augmented with amphotericin B, 100 mg. per day, given intravenously.

On 25 October, his downward course, manifested by increasing fever and pulse rate, lapse into deep coma and spread of necrosis, indicated that operation to remove gangrenous tissue was necessary for his survival even though he was an extremely poor surgical risk.

The operation, consisting of midline extirpation, en bloc, of the left maxilla combined with bilateral ethmo-sphenoidectomy, disclosed widespread necrosis of: the left cheek flap (including muscle), the left ala nasi (now black) and maxillary sinus, both ethmoid sinuses, the nasal septum and the sphenoid sinus. The right inferior turbinate appeared necrotic, so the right maxillary sinus was explored. Its mucosa was hyperplastic but extremely vascular.

After surgery, insulin requirements diminished dramatically, and he required no insulin after 9 November 1960.

On 29 October, thrombosis of the left central retinal vessels was apparent. On 7 November, he developed right hemiplegia, which we attributed to thrombosis of the left internal carotid artery. On 12 and 13 November, because of fever peaks of 105°, blood and sinus washings were cultured; both yielded beta-hemolytic streptococcous *and Staphylococcus aureus,* so we began treatment with 30 million units of penicillin daily. He improved gradually. Culture of spinal fluid at this time was sterile although the fluid contained 142 leukocytes per c.mm., of which 66% were lymphocytes. Two other spinal fluid cultures revealed no bacteria or fungi.

Penicillin was continued until 2 December, when cultures of urine and sinus washings revealed heavy growth of Pseudomonas. Therefore, penicillin was replaced by intravenous chloramphenicol and intramuscular polymyxin B.

On 8 December, his rectal temperature suddenly ascended to 105.8° (after ranging between 100° and 102.4° for 6 days), and he began spewing bright blood through the tracheostomy tube. We found signs of bilateral pneumonia. Cultures of blood and sputum on this day yielded *Staphylococcus aureus.* Intravenously given penicillin (30 million units per day) was added to his treatment. He did not improve, so chloramphenicol and polymyxin were discontinued on 12 December; and on 13 December penicillin was replaced by dimethoxyphenyl penicillin (Staphcillin), with rapid improvement.

The patient survived other complications. At the time of writing (7 months after onset of illness) he can walk with the aid of a

TABLE 1.—ANTIBIOTIC THERAPY

Antibiotic	*Indication*	*Date Begun*	*Date Discontinued*
Chloramphenicol	Urinary tract infection (Aerobacter)	13 Oct 1960	20 Oct 1960
Penicillin	Sinusitis	20 Oct	21 Oct
Streptomycin	(organism unknown)	20 Oct	22 Oct
Polymyxin B	Sinusitis (Pseudomonas)	21 Oct	26 Oct
Amphotericin B	Mucormycosis	24 Oct	14 Nov
Penicillin	Septicemia (beta-hemolytic streptococcus and *Staphylococcus aureus*)	14 Nov	2 Dec
Chloramphenicol Polymyxin B	Sinus & Urinary Infection (Pseudomonas)	2 Dec	12 Dec
Penicillin	Pneumonia & Septicemia (*Staphylococcus aureus*)	8 Dec	13 Dec
Staphcillin	Pneumonia & Septicemia *(*Staphylococcus aureus*)	13 Dec	30 Dec

*Positive Culture despite penicillin.

brace and a cane, but has no motion of the right upper extremity; his left eye does not perceive light. A prosthesis occludes the palatal and facial defects. He weighs 170 pounds, receives no insulin and has no glycosuria.

COMMENT. Rhizopus and other fungi of the Mucorales order are found on normal skin, on fruit and other foods, and are common laboratory contaminants. Given antecedent conditions discussed below, these ordinarily saprophytic fungi can become amazingly invasive, penetrating walls of arteries and other tissues and producing arterial occlusions. Another peculiarity which distinguishes Rhizopus from almost all other fungi is its ability to produce acute rather than chronic disease.

The pathology of mucormycosis was described in a classic article by Paltauf and recently in reports by Neame and Raynor[6] and McBride, Corson and Dammin[5]. The latter, published in 1960, includes a table of 56 "acceptable cases of mucormycosis" which have been reported in the English literature. The mycology and pathology were excellently described by Bauer and coworkers[1].

Rhizopus did not disappear after Paltauf's report almost 80 years ago; and diabetes, leukemia, uremia and ulcerative intestinal disease (antecedents for almost all cases of human mycormycosis) have affected innumerable patients since then. But, strangely, the first report of cases (Gregory, Golden and Haymaker[4]) in this country did not appear until 1943, after the introduction of sulfanilamide and other potent systemic antimicrobials.

The extremely rare occurrence of mucormycosis despite the prevalence of the essential ingredients, fungi and predisposing diseases, suggests that a "catalyst" is required. Antibiotics and antimetabolites are, we believe, the chief "catalysts." The former affect bacterial flora in body cavities, destroying bacteria which inhibit fungi and favoring bacteria which may facilitate invasiveness of fungi. It is noteworthy that when Osswald and Seeliger[7] produced experimental mucormycosis, they treated mice with tetracycline before injecting them with *Mucor pusillus* because other investigators had reported that such preparation facilitated fungal infection.

The administration of antibiotics preceded the onset of mucormycosis in both of our patients. Neame and Raynor, reporting from Africa, stated that all of their 22 cases had received antibiotics; and, as far as we can analyze reports with adequate clinical data, almost every patient reported in the American literature may have received antimicrobials or antimetabolites before the onset of mucormycosis. However, Bauer and associates may be correct in their belief that some antibiotics may be useful because bacterial infection appears to be a predisposing factor. Several authors have reported histologic evidence of severe and polybacterial invasion of tissues also invaded by Rhizopus despite (or because of) use of antibiotics (Bauer *et al.*[1], Stefanini and Allegra[10]).

Mucormycosis occurs in several localized forms: cranial, pulmonary and intestinal. The first, which is most frequent and which is particularly associated with diabetes, begins as a sinus infection. The fungus rapidly invades adjacent tissues and produces orbital infection, circumocular swelling, proptosis and ophthalmoplegia. Infection and necrosis of meninges and brain may be caused by direct extension from orbit or sinus or by septic thromboses of the carotid artery or its branches. The *pulmonary* form clinically and roentgenographically resembles pneu-

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monia, abscess or infarct; and it is the most frequent form in leukemic patients (Stefanini and Allegra[10]). The *intestinal* form of mucormycosis produces hemorrhagic infarctions of small or large intestine. Other organ involvement is rare. Prout and Goddard recently reported a case of renal localization[9].

Diagnosis of cranial mucormycosis will be facilitated by recognizing the following clinical clues. The setting is acute sinusitis in a diabetic patient. The signposts are: (1) increasing swelling and redness despite administration of antibiotics (or use of antibiotics preceding sinusitis); (2) proptosis; (3) the paradox of increasing infection and decreasing pain; (4) affection of cranial nerves without signs of cavernous sinus thrombosis; (5) facial anesthesia; (7) unsuccessful aspiration of the maxillary sinus, when physical signs and roentgenograms indicate that pus should be obtained; (8) abnormally little, or no, bleeding when the face is incised.

Culture of bacteria from sinus aspirate does not militate against mucormycosis. Demonstration of the characteristic broad, branching, nonseptate hyphae within the lesions is necessary for diagnosis; it is desirable to demonstrate the fungi, usually of the genus Rhizopus, in cultures of tissue obtained for biopsy.

The second patient's recovery was attributed to amphotericin B and surgery. He survived several serious complications including one episode of staphylococcal pneumonia and septicemia and one of staphylococcal *and* streptococcal septicemia. Treatment with amphotericin was initiated despite hyperazotemia, lasted 22 days (2.2 gm. were given), and ceased when the first episode of septicemia was diagnosed. Its use was accompanied by decrease of hyperazotemia. The first patient was seen before amphotericin B was available.

Summary. Mucormycosis, an uniquely acute, usually fatal infection by fungi of the order Mucorales, may occur in patients with diabetes or leukemia. We believe that antibiotics given to the former, and antimetabolites to the latter, act as "catalysts" to effect infection by these ordinarily harmless saprophytes.

Two cases of cranial mucormycosis are reported. The clues to early clinical diagnosis are described. The first was in an uncontrolled, but not acidotic, diabetic who had been taking antituberculosis drugs. The second case developed in a diabetic in acidosis who had been receiving chloramphenicol for an infection of the urinary tract.

Recovery of the first patient followed surgery and is not attributable to medication. Recovery of the second patient is attributed to treatment with amphotericin B and surgery.

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(Interlingua on page 410)

THE PROGNOSIS OF TUBERCULOUS MENINGITIS IN THE ISONIAZID ERA

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In a previous report[6], the authors presented data to show the tremendous impact of isoniazid on the therapeutic results of tuberculous meningitis at the Philadelphia General Hospital. We pointed out that as more patients with this disease survive, it becomes feasible to describe the clinical factors which influence the outcome. The important prognostic factors in 41 cases treated during the period 1952 to 1954 seemed to be limited to age and the initial cerebrospinal fluid chloride concentration. With the addition of 32 more cases in the period 1955 to 1957 we are now in a position to make some comment on several additional factors in our material which relate to prognosis.

Method and Material. The hospital records of all patients discharged with a diagnosis of tuberculous meningitis and treated with a regimen containing isoniazid between 1952 and 1957 were reviewed. There was a total of 74 acceptable cases. The minimal requirements for inclusion of cases in this series were a lymphocytic type of cerebrospinal fluid reaction, clinical picture, and course compatible with the diagnosis of tuberculous meningitis. Table 1 presents the evidence of proved diagnosis in this series according to survival. It can be seen that tubercle bacilli were found in the cerebrospinal fluid of 56% of the patients and that an additional 25% showed bacteriologic or histologic evidence of active tuberculosis elsewhere in the body; therefore, tuberculosis was proved in 81% of the 73 cases. Evidence of tuberculosis was obtained in 89% of those who died and in 71% of those who survived. This is a barely significant difference but it was partly due to the fact that 3 of the deaths yielded proof only on necropsy; otherwise the differences are not statistically significant.

Table 2 shows the drugs which were used to treat the patients, according to 3-year periods and to survival. Dosage and duration of therapy were those commonly accepted at the time. All of the patients in this study received isoniazid and all but one received streptomycin as well. Para-aminosalicylic acid (PAS) was often avoided in both periods among those who died because of the necessity for large parenteral doses. However, in the second 3-year period there was a tendency to depend on isoniazid and streptomycin alone, even in patients who were able to take oral medication. In recent years, this tendency has increased and now sometimes double drug regimens are employed, using streptomcin with isoniazid during hospitalization and substituting PAS for streptomycin on discharge because of the convenience of oral therapy during outpatient management. Intrathecal streptomycin was used in 11 patients during the first period, all of these being children on the pediatric wards, but was abandoned completely in the second period. Drug susceptibility

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TABLE 1.—PROOF OF TUBERCULOSIS IN 73 PATIENTS WITH MENINGITIS

	In 38 Pts. Who Died		*In 35 Pts. Who Lived*		*Totals*	
	No.	*%*	*No.*	*%*	*No.*	*%*
Positive CSF for AFB	23	61	18	51	41	56
Other cases proved by extrameningeal proof, including necropsy	11*	29	7	20	18	25
Total Cases Proved	34	89[1]	25	71[1]	59	81

[1]P<0.05
*3 Cases proved by necropsy only

TABLE 2.—ANTIMICROBIAL THERAPY

	41 Cases 1952–1954		*32 Cases 1955–1957*	
	Died	*Lived*	*Died*	*Lived*
Isoniazid	23	18	15	17
Streptomycin	23	18	14	17
Para-aminosalicylic acid	16	17	6	11

TABLE 3.—POSSIBLE CLINICAL FACTORS IN PROGNOSIS OF TUBERCULOUS MENINGITIS

	38 Pts. Who Died		*35 Pts. Who Lived*		*Total: 73 Pts.*	
Factor	*No.*	*%*	*No.*	*%*	*No.*	*%*
Age, years						
0–10	4	11	13	37	17	23
11–40	14	37	18	51	32	44
41 plus	20	53	4	11	24	33
Race—Negro	37	97[1]	27	77[1]	64	88
Sex—Male	21	55	14	40	35	48
Duration before admission						
less than 1 week	12	32	7	20	19	26
1–2 weeks	12	32	13	37	25	34
over 2 weeks	7	18	7	20	14	19
Unknown	7	18	8	23	15	21
Comatose	4	11	6	17	10	14
Complications						
A. tuberculous	35	92[2]	25	71[2]	60	82
1. miliary	17	45	14	40	31	42
2. pulmonary	23	61	15	43	38	52
3. other	11	29	6	17	17	23
B. nontuberculous	8	21	4	11	12	16
Previous Meningitis	1	3	2	6	3	4
Therapeutic						
A. steroid hormones	10	26	6	17	16	22
B. intrathecal streptomycin	1	3[3]	11	31	12	16
Cerebrospinal Fluid Block	4	11	3	9	7	10
Sequelae, neurologic	—	—	10	29	—	—

[1]P<0.01
[2]P<0.05
[3]P<0.01

tests were not done as a routine procedure on isolates from the cerebrospinal fluid or other secretions.

Results. The entire series of 73 patients has been divided into two groups; those who died and those who survived. These two groups have been compared with respect to certain clinical factors which might or might not be related to prognosis (Table 3).

Age was a most important factor; the majority (76%) of the children survived, about one-half (56%) of the young adults, but only 17% of the patients over the age of 40 survived. This is illustrated by figures in Table 3 showing that 53% of the deaths were in the oldest age group, whereas the vast majority of the survivors were in the younger age groups. Race was also a statistically significant factor; 97% of the deaths occurred in non-whites, whereas 77% of the patients who lived were non-whites. Sex bore no definite relation to outcome in this series; neither did duration of symptoms prior to admission, nor the presence of coma.

The occurrence of extrameningeal tuberculosis of all forms had a significant relation to prognosis but miliary tuberculosis seemed to be equally as common among the patients who died as in those who survived. Previous tuberculous meningitis (prior to the isoniazid era) had occurred in one of the patients who died and in 2 who lived.

Two therapeutic factors were considered. The use of steroid hormones had no significant relationship to the mortality rate. This will be discussed at length below.

Intrathecal streptomycin seemed to bear a highly significant relation to outcome, in that only 3% of the deaths received this treatment whereas 31% of the survivors were so treated. However, it should be remembered that this form of treatment was employed only in children in this series and in them only during the first 3-year period. The survival rate of children did not change significantly in the second 3-year period. During 1952 to 1954, 8 of 11 children survived (73%) and during 1955 to 1957, 5 of 6 survived (83%). It is, therefore, likely that age is the common factor which makes intrathecal streptomycin appear to be related to prognosis. Furthermore, neurological sequelae occurred in 10 of the 35 survivors. When we divide the survivors among the two 3-year periods, we find that in 1952 to 1954, *7 of 18 survivors had sequelae and 5 of the 7 had received intrathecal streptomycin. Thus,*

TABLE 4.—INITIAL CEREBROSPINAL FLUID FINDINGS

	Patients Who Died			*Patients Who Lived*			*Totals*		
	No. Tested	*No.*	*%*	*No. Tested*	*No.*	*%*	*No. Tested*	*No.*	*%*
Opening Pressure	24			26			50		
<200 mm. Hg		7	29		8	31		15	30
>400 mm. Hg		4	17		7	27		11	22
Protein >300 mg./100 ml.	32	8	25[1]	31	1	3[1]	63	9	14
Chlorides <585 mg./100 ml.	28	11	39[2]	31	3	10[2]	59	14	24
Sugar <20 mg./100 ml.	34	9	26	31	5	16	65	14	22
Cells >200/c.mm.	34	17	50	33	14	42	67	31	46
Tubercle bacilli	34	22	65	35	19	54	69	41	59

[1]$P<0.02$ [2]$P<0.01$

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2 of 13 survivors who did not receive intrathecal streptomycin had sequelae. In 1955–1957, only 3 of 17 survivors had neurological sequelae and none received the drug in intrathecal form. These figures suggest that perhaps intrathecal medication was sometimes related to neurological sequelae, although the numbers are too small to permit a definite conclusion. Cerebrospinal fluid block occurred in too few cases (10%) to have any bearing on mortality rate.

In Table 4, some pertinent findings are given in the initial cerebrospinal fluid examinations among those patients who died compared to those who lived. Only two of these findings showed a significant difference between the groups: Patients who survived seldom showed a protein concentration above 300 mg. per 100 ml. or a chloride concentration below 585 mg. per 100 ml., whereas 25% of the deaths showed such high protein measurements and 39% showed such low chloride determinations.

Mortality rates for the two 3-year periods are shown in Table 5. In 1952 to 1954, 56% of 41 patients died. In 1955 to 1957, 47% of 32 patients died. This difference is not statistically significant but as more cases are accumulated a diminishing mortality rate may appear. The incidence of the disease also seems to be decreasing, but figures are insufficient to be sure of this as yet.

TABLE 5.—MORTALITY RATES BY PERIOD

	Total	*Died*	
	No.	*No.*	*%*
1952–1954 Cases	41	23	56
1955–1957 Cases	32	15	47
Totals	73	38	52

Follow-up information was obtained in 31 of the 35 patients who were discharged alive. The total period of observation from admission varied from 20 to 54 months. One patient was transferred to a state psychiatric hospital after 10 weeks because of paranoid schizophrenia when the meningitis improved; he died 4.5 months later and death was attributed to tuberculous meningitis, although no proof of this was obtained. A second patient died in another hospital 35 months after onset of her disease and death was attributed to *pneumococcal* meningitis. Two others have died of non-tuberculous causes, 45 and 52 months after admission. Figures on the total duration of therapy are not available but treatment is usually planned for 2 years or more.

When death occurs, it usually does so during the first month, as can be seen in Fig. 1. This shows the survival curve during the first 20 months after diagnosis is made: Almost all deaths attributable to meningitis occurred during the first month and all but one during the first 2 months. After that, survival is practically certain. Four patients were lost to observation.

Discussion. In the isoniazid era, the most important prognostic factor in survival following tuberculous meningitis is age. According to the way we have divided our age groups, older patients have a very poor prognosis and children have an excellent outlook. Race is also a significant factor in favor of the white patients. Sex does not appear to be a significant factor. Other insignificant factors in our data include the duration of illness before admission and the state of consciousness on admission to the hospital. These are both important factors, according to other authors. However, it should be pointed out that the onset of tuberculous meningitis is difficult to date by history of symptoms with any real degree of reliability. We are unable to explain why other investigators find the state of consciousness to be im-

portant in relation to survival and we are unable to substantiate this.

Extrameningeal tuberculosis of all forms is a factor of some importance, although the finding of miliary tuberculosis itself is not. The probable reason for this is that the prognosis of miliary tuberculosis itself is so good in the absence of meningitis.

has been a suggestive indication of a decrease in neurologic sequelae among survivors. None of these changes in therapeutic method has occurred at this institution under controlled conditions; they have simply represented trends in medical management growing out of clinical experience, with the exception of steroid therapy.

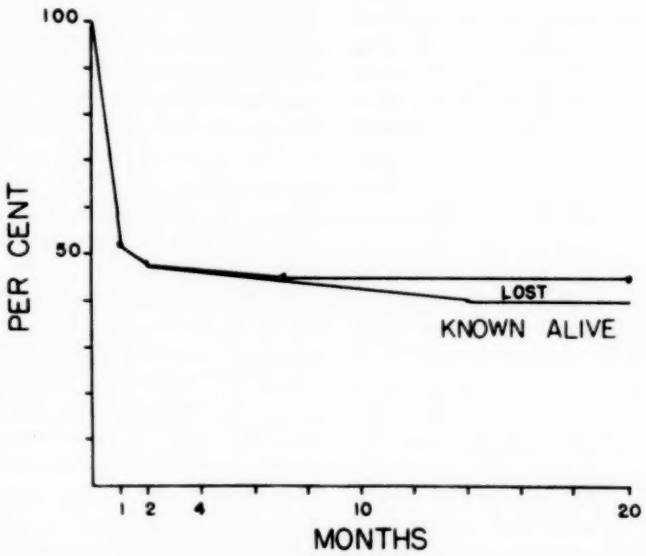

Fig. 1.—Survival curve of patients with tuberculous meningitis in the isoniazid era. Percentage known to be alive is plotted in the lower curve. The area between the two curves represents 4 cases lost to follow-up.

The only important prognostic signs in the initial cerebrospinal fluid examination are the height of the protein content and the diminution in the chloride concentration.

Several changes have been made in therapeutic methods during the isoniazid era. These include a tendency to use double drug therapy, the abandonment of intrathecal streptomycin, and the addition of steroid hormones. Despite these changes, there has been no significant change in survival rates in our data. However, with the abandonment of intrathecal streptomycin, there has been a suggestive indication of a decrease in neurologic sequelae among survivors. None of these changes in therapeutic method has occurred at this institution under controlled conditions; they have simply represented trends in medical management growing out of clinical experience, with the exception of steroid therapy.

This latter treatment has seemed to spring from the effect of a few uncontrolled reports in the literature with a tenuous theoretical rationalization as their basis. The rationalization is as follows: (1) steroid hormones help to support a critically ill patient because of their "antitoxic" effects and tide the patient over a life-threatening period until the antimicrobial agents take hold, and (2) steroid hormones limit the formation of granulation tissue and fibroblastic proliferation, effects which prevent or relieve cerebrospinal fluid block.

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While this rationalization has been attractive to many practicing physicians, it is unsupported by attempts at well controlled studies in tuberculous meningitis. To our knowledge, there has been only one small attempt at a controlled investigation of steroids in the treatment of this disease by Lepper and Spies[3] involving the alternation of cases and it failed to show any significant effect on survival. Ashby and Grant[1] tried a comparison of two groups of 6 patients each but the cases were not chosen at random or alternated, and therefore their conclusion that steroids are valuable in therapy is open to question. Chance alone could easily account for the differences they reported in such minute groups.

While there is an absolute indication for steroid hormones in cases in which such hormonal deficiency is reasonably suspected or proved, it is unworthy of the medical profession to allow itself to fall prey to therapeutic fads. This was once succinctly emphasized by Perry Pepper and recently reiterated by Middleton[4]. An important reason for skepticism of this form of therapy lies in the second Hippocratic principle: "If you can do no good, at least do no harm." The literature on steroid hormones is replete with descriptions of the various kinds of harm which result from the use of these powerful agents. Therefore, caution in their administration is in order. In the particular case of tuberculous meningitis there is the danger, small though it be, that one may be treating a patient whose organisms are resistant to the antimicrobial agents in use. In such a case, steroids may obscure a failure to respond to therapy, which would indicate a change in antimicrobial drugs, and thus lead to a preventable death. This again may be rationalization, but the possibility exists.

A tendency to use steroid hormones in cases of tuberculous meningitis has developed in recent years at this institution among certain physicians, as elsewhere. Some physicians use the hormones in all cases, others in only critically ill patients, and a few physicians with sufficient skepticism and intellectual fortitude do not use the hormones unless there is reason to believe that substitution therapy is needed for adrenal insufficiency. In contrast, there are some hospitals where steroid hormones have become routine therapy. For example, Voljavec and Corpe[5] recently presented the results in 33 Negroes with moderate and severe tuberculous meningitis, 16 of whom received steroids in addition to antimicrobial drugs. This was an uncontrolled study of patients in the isoniazid era. These patients were collected over a 6-year period and the two groups of patients were formed only because the frequency of use of steroids in meningitis gradually increased. The mortality rates in these two groups differed by a barely statistically significant degree in favor of the steroid group. The authors designed a prognostic index which was alleged to show that the two groups were comparable except that there were more cases of cerebrospinal fluid block in the steroid group. They concluded that "corticosteroid hormones used with isoniazid, streptomycin, and PAS are extremely valuable in the treatment of advanced cases of tuberculous meningitis, particularly when used early and in the presence of cerebrospinal block." This conclusion is unwarranted because the study did not use concurrent controls.

Time itself reflects the operation of known and unknown factors which may influence the results of treatment. In Table 5 we have shown a small, though statistically insignificant, fall in the mortality rate during the isoniazid era at The Philadelphia General

Hospital. The fall in mortality rates at other hospitals may be more significant and yet not be related to a specific therapy. The design of a prognostic index is no substitute for a concurrently controlled study in which the cases are chosen at random. We have tried to show this in Table 6.

We have considered the data in 28 Negroes with moderate and severe tuberculous meningitis treated at our hospital during the 1955 to 1957 period and comparison is made with the series of Voljavec and Corpe. The number and distribution of cases between the steroid and standard therapy groups were approximately the same in both series, and so was the average prognostic index. Yet, we have a slightly higher mortality rate in our steroid group than in our standard treatment group. Obviously, there is a serious discrepancy between the results of Voljavec and Corpe compared with our results. Since both series present observations of uncontrolled groups, it is fruitless to argue the merits of one series versus those of another series. There are obvious discrepancies in method and perhaps material but there may also be unknown factors to explain differences in results.

It is apparent that steroid hormone therapy cannot be accepted as routine therapy for tuberculous meningitis. In fact, it should be considered a controversial subject until a large scale controlled study is done. Because the disease is uncommon, such a study is possible only with cooperation of a number of hospitals, such as those carried out by the Veterans Administration or the U.S. Public Health Service. On the other hand, some physicians have had the experience in one or more cases in which steroid hormone therapy has seemed to be associated, in intermittent courses, with corresponding clinical and cerebrospinal fluid changes which favor the use of these drugs in certain cases. We have seen this happen in at least one patient and Johnson *et al.*[2] have reported the phenomenon in several cases. It is not clear what kind of cases of meningitis has a real requirement for hormonal support but it is likely that the number of such cases is small.

TABLE 6.—EFFECT OF STEROID HORMONE THERAPY ON MORTALITY RATE OF TUBERCULOUS MENINGITIS IN NEGROES

	Volvajec and Corpe Therapy		*Weiss and Flippin Therapy*	
	Standard	*Steroids*	*Standard*	*Steroids*
No. of Cases	17	16	16	12
Average Prognostic Index in Points	4.4	4.9	4.2	4.3
No. of Deaths	9	3	8	7
% Mortality	53[1]	19[1]	50	58

[1]$P<0.05$

Summary. Seventy-three patients with tuberculous meningitis treated with a drug regimen containing isoniazid from 1952 to 1957 have been reviewed. Tubercle bacilli were found in 56% and proof of active extrameningeal tuberculosis was found in an additional 25%. There has been a growing tendency to use double drug, rather than triple drug therapy. This series was studied for significant prognostic factors. These include age, race, the pres-

ence of extrameningeal tuberculosis (excluding miliary tuberculosis), cerebrospinal fluid protein, and chloride concentrations.

Intrathecal streptomycin was found to be of no value and might have caused some neurological sequelae among survivors. It was abandoned. Recurrence of meningitis after clinical cure did not occur during a follow-up period of 20 to 54 months.

With the evidence at hand, steroid hormone therapy cannot be accepted as a routine measure for the management of tuberculous meningitis. Until concurrently controlled large scale investigations actually show an advantage to the use of these potent hormones, they should be reserved for patients with suspected or obvious hormonal deficiency.

ACKNOWLEDGMENT: The authors are grateful to William J. Carnahan, Statistician, Philadelphia Tuberculosis and Health Association, for determinations of statistical significance of differences.

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SUMMARIO IN INTERLINGUA

Le Prognose de Meningitis Tuberculotic in le Era de Isoniazido

Esseva revistate le casos de 73 patientes con meningitis tuberculotic tractate inter 1952 e 1957 con un regime chimotherapeutic a contento de isoniazido. Bacillos de tuberculosis esseva trovate in 56%, e provas de active tuberculosis extrameningee esseva trovate in 25% additional. Le tendentia ha crescite de usar therapias a droga duple plus tosto que a droga triple. Le presente serie esseva studiate pro significative factores prognostic. Istos include etate, racia, le presentia de tuberculosis extrameningee (con le exclusion de tuberculosis miliari), proteina del liquido cerebro-spinal, e concentration de chloruro.

Esseva trovate que streptomycina intrathecal es sin valor. Il es possibile que illo esseva responsabile pro certe sequellas neurologic inter le superviventes. Su uso esseva abandonate. Recurrentias de meningitis post curation clinic non esseva incontrate durante le periodos de observation catamnestic de inter 20 e 54 menses.

A base del datos nunc disponibile, therapia a hormon steroide non pote esser acceptate como mesura routinari in le tractamento de meningitis tuberculotic. Usque simultanee investigationes controlate in massa demonstra de facto un avantage resultante del uso de iste potente hormones, illos deberea esser reservate pro patientes con suspicite o obvie carentias hormonal.

THE RELIABILITY OF "ARTERIALIZED" VENOUS BLOOD FOR MEASURING ARTERIAL pH AND pCO_2

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The acid base balance of blood in health is maintained within narrow limits. Metabolic and respiratory disturbances disrupt this balance, but unfortunately the type of imbalance frequently cannot be recognized and its degree never quantitated on clinical grounds alone. Yet such imbalances must be quickly recognized and corrected because gross disturbances are incompatible with life. It is for these reasons that quantitative chemical analysis of the arterial blood is essential for rational therapy of acid base disturbances and for following the effects of treatment.

Venous blood is disadvantageous for such studies because its content of pH and pCO_2 varies with its site of origin and with the underlying metabolic disturbances of the tissue or organ from which the vein drains. Recently it has been suggested that "arterialized" venous blood has an acid base balance identical with that of arterial blood (Wynn[2]). This study was made to determine the validity of this statement.

Methods and Material. Twenty-nine consecutive hospitalized subjects, all free of fever and of overt heart failure, age 27 to 72 years, were chosen for study. All had been recumbent for at least one and one-half hours before blood was drawn for analysis. The hand was warmed by a hot towel or a hot water container for 15 to 20 minutes before blood was drawn from a vein on the dorsum of the hand.

Three techniques were used. In 15, a tourniquet was applied above the elbow and the arm was at bed level. In 6 of these 15, a 10-ml. vacuum tube was used for collection of blood from a vein on the dorsum of the hand. In the other 9 of these 15, heparinized syringes were used for this collection. In 14 additional subjects, a tourniquet was applied at the wrist with the hand laid on the bed. If the veins filled within 60 seconds, venesection was performed. In only 50% did such filling occur. In the latter 50%, flexion of the fingers several times was required to produce filling of the veins.

A 22 gauge needle was used for obtaining blood from a vein on the dorsum of the hand, and also for obtaining arterial blood. A 20 gauge needle was used for the conventional venous sample. One to 2 ml. of blood was drawn from each site.

Astrup's micromethod was used to determine pH and pCO_2 (Siggaard Andersen *et al.*[1]); the pH was determined within a few minutes and pCO_2 equilibrations within one hour of the withdrawal of blood. Radiometric certified buffer batch #331 was the primary standard with a pH of 7.381; the secondary standard was 0.05 M p-Nitrophenol adjusted to a pH of 7.3.

Results. The use of vacuum tubes was found unsatisfactory because no more than 1 to 2 ml. of blood could be obtained from the vein on the dorsum of the hand. Furthermore, this method gave the greatest discrepancy of the three between "arterialized" venous and arterial blood. The pH difference between these two sites by this method was 0.050 and the pCO_2 difference 4.9 mm. Hg.

The use of a heparinized syringe for drawing blood from a vein on the dorsum of the hand and after a tourniquet had been applied above the elbow was superior to the use of vacuum tubes. The pH difference between arterial and "arterialized" venous blood was 0.038 and that of pCO_2 8.5 mm. Hg. Neither of these two methods, however, was as good as drawing blood from a vein on the dorsum of the hand with the tourniquet placed just above the wrist.

The data for the last method are presented in Table 1 and scattergrams of the pH and pCO_2 in Figs. 1 and 2 respectively.

Note that on the average, the pH of the "arterialized" venous blood is 0.022 and that of the pCO_2 2.86 mm. Hg lower than that of arterial blood. The standard error of deviation in the Astrup method of determining pH is 0.006. The error for the pCO_2 determination depends upon where the pH of the sample lies in relationship to the CO_2 equilibration points: if it lies between these points, the error is 0.5%; but if it lies outside these points, the error is 2 to 3%.

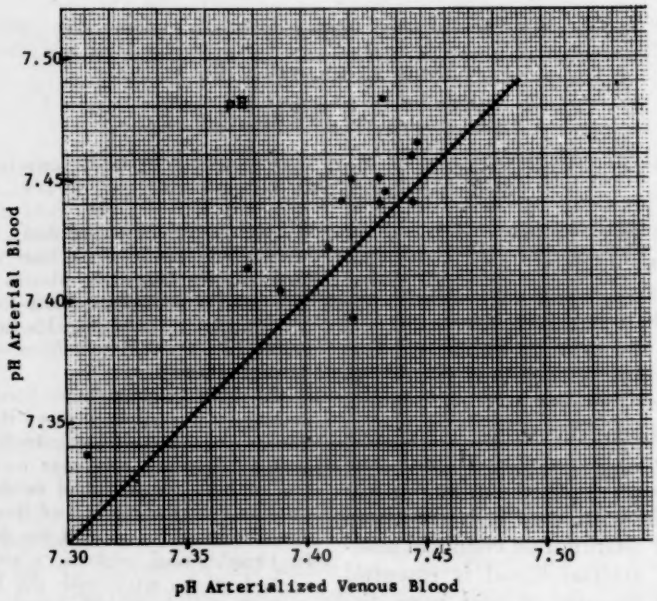

Fig. 1.—Scattergram of arterial and "arterialized" venous pH.

It should also be noticed that the "arterialized" venous pH and pCO_2 determinations were closer to the arte-

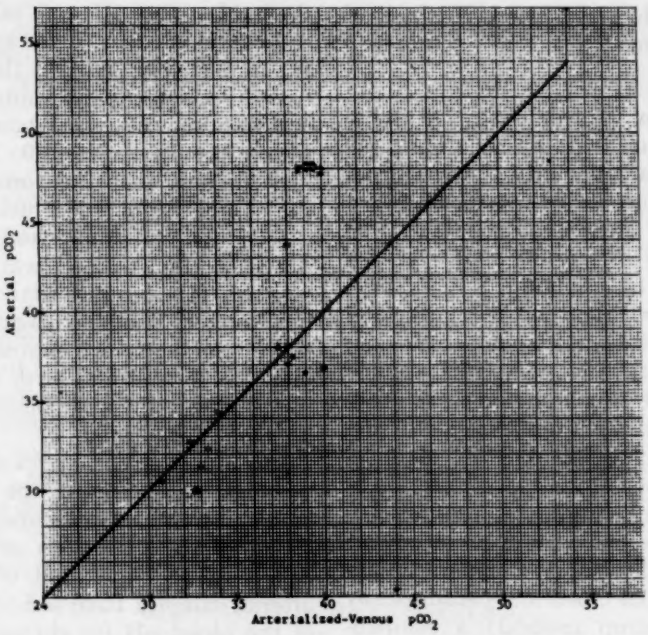

Fig. 2.—Scattergram of arterial and "arterialized" venous pCO_2.

TABLE 1.—DATA ON pH, pCO_2 AND STANDARD BICARBONATE OBTAINED BY USE OF HEPARINIZED SYRINGE FOR DRAWING BLOOD FROM A VEIN ON THE DORSUM OF THE HAND WITH THE TOURNIQUET APPLIED IMMEDIATELY ABOVE THE WRIST

	Age	pH			pCO_2			Standard Bicarbonate		
		Arterial Blood	Arterialized Venous Blood	Venous Blood	Arterial Blood	Arterialized Venous Blood	Venous Blood	Arterial Blood	Arterialized Venous Blood	Venous Blood
F.E. S.V.C. Syn.	59	7.484	7.433	7.435	36.7	40.0	39.1	27.1	25.7	25.5
C.R. CVA	72	7.452	7.433	7.410	24.5	44.0	30.5	21.4	21.7	19.9
W.B. Ch. Pul. Dis.	59	7.338	7.308	7.269	57.0	54.0	62.0	27.5	25.2	25.3
J.W. Fx. mandible	44	7.394	7.420	7.382	43.5	38.0	43.3	25.0	24.0	24.0
G.V. Ch. Pul. Dis	56	7.440	7.432	7.416	32.3	33.4	36.5	22.5	23.1	23.0
M.G. Peptic Ulcer	68	7.421	7.410	7.382	37.4	38.2	42.8	23.6	23.7	24.0
C.J. Tietze's Syn.	50	7.460	7.446	7.416	34.5	35.0	38.4	25.2	24.1	24.1
G.D. Diabetes	55	7.442	7.416	7.376	38.0	37.5	43.5	25.4	23.6	24.0
J.S. Gout	38	7.448	7.409	7.365	30.5	30.8	31.0	22.5	20.5	18.8
J.B. Tabes	66	7.440	7.447	7.424	32.7	32.3	34.6	22.5	22.9	23.0
B.W. CVA	70	7.405	7.390	7.402	38.0	38.0	36.3	23.2	22.5	22.4
T.B. CHF & Pneumonia	72	7.445	7.432	7.380	36.5	39.0	45.3	24.9	25.3	24.8
J.T. RHD	22	7.411	7.378	7.374	31.3	33.0	33.0	21.0	20.2	19.9
J.McM. Cirrhosis	56	7.467	7.448	7.403	37.0	38.0	42.0	22.8	23.5	25.0

Average (arterial pH - "arterialized-venous" pH) = 0.0222 Average (arterial pH - venous pH) = 0.1100

Average (arterial pCO_2 - "arterialized-venous" pCO_2) = 2.86 Average (arterial pCO_2 - venous pCO_2) = 3.40

rial value than they were to those of blood obtained from an antecubital vein.

Discussion. It should first be noted that it is not always possible to obtain blood from a vein on the dorsum of the hand without at least minimal stasis of that vein and without a few flexions of the fingers. Warming of the hand is necessary to obtain "arterialized" venous blood and this blood is most nearly arterialized if minimal stasis is accomplished by a tourniquet applied at the wrist. Even under these ideal conditions, the pH and pCO_2 of "arterialized" venous blood is not identical with that of arterial blood. In those in acid base balance, the "arterialized" venous blood will still show an apparent minimal acidosis compared with that of arterial blood and paradoxically (by the Astrup method) a compensated respiratory alkalosis. The differences from arterial blood, however, are not great. The arterial values can be estimated by adding 0.022 to the pH value and 2.86 mm. Hg to the pCO_2 value. "Arterialized" venous blood, therefore, can be used as a clinical guide to determine whether the subject is in acid base balance. If the subject is in acid base balance, "arterialized" venous blood may also be used to determine the directional changes of the acid base balance produced by subsequent changes in the clinical status of the patient or by treatment.

However, "arterialized" venous blood may be most difficult to obtain when the pH and pCO_2 determinations are most urgently needed as in shock and in respiratory alkalosis. Under such circumstances, however, venous blood from the antecubital vein has a pH and pCO_2 content extremely close to that of the arterial and is even more reliable than that of "arterialized" venous blood. Thus, in a patient with respiratory acidosis not included in the tables, the pH and pCO_2 of the arterial blood was 7.059 and 95 mm. Hg respectively; whereas that of blood from the antecubital vein was 7.062 and 98.5 mm. Hg. The standard bicarbonate for each was 18.0. These findings suggest that the forearm under these circumstances has little metabolic activity; on the other hand, the "arterialized" venous blood was 7.087 and 85 mm. Hg and the standard bicarbonate 18.1. They also, again paradoxically, suggest an unavoidable but clinically insignificant error in the technique of withdrawing blood from the dorsum of the hand.

It is unfortunate that, for many years, technical limitations of the glass electrode instruments and undue emphasis upon the difficulties of anaerobic collection of blood and of obtaining arterial samples have led to a neglect of the blood pH for clinical purposes.

From the present study, it would appear that even in instances in which rather large arteriovenous differences might be expected, the "arterialized" sample obtained from the veins on the dorsum of the hand of a "warmed" extremity is entirely justified for the estimation of blood pH. Furthermore, in clinical states where the metabolic activity of the extremity is depressed, a sample obtained from any vein of that extremity is suitable.

Conclusions. 1. "Arterialized" venous blood for estimation of the blood pH is best obtained from a vein on the dorsum of the hand after warming the hand for 20 minutes and after applying a tourniquet to the wrist and flexing the fingers for a moment or two.

2. "Arterialized" venous blood so obtained in subjects in acid base balance has, on the average, a pH value 0.022 and a pCO_2 2.86 mm. Hg lower than that of arterial blood.

3. Samples from "arterialized" venous blood are, therefore, justified for the estimation of arterial pH.

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SUMMARIO IN INTERLINGUA

Le Fidelitate del "Arterialisate" Sanguine Venose in le Mesuration del pH e del pCO_2 Arterial

1. Specimens de "arterialisate" sanguine venose pro le estimation del pH del sanguine se obtene le melio ab un vena al dorso del mano post calefacer le mano durante 20 minutas e post applicar un tourniquet al carpo e flecter le digitos durante un momento o duo.

2. Le "arterialisate" sanguine venose assi obtenite ab subjectos in balancia acido-basic ha, al media, un pH 0,022 mm de Hg infra illo de sanguine arterial e un pCO_2 2,86 mm de Hg infra le pCO_2 de sanguine arterial.

3. Le uso de specimens de "arterialisate" sanguine venose es, per consequente, justificate in le estimation de pH arterial.

SUMMARIO IN INTERLINGUA

(See page 411 for original article)

Amino-Aciduria in Intoxication per Salicylato

Cinque patientes, sub observation a causa de intoxication per salicylato, esseva studiate pro le presentia de amino-aciduria. In 4 patientes con nivellos sanguinee de salicylato in supra del usual limites therapeutic, un generalisate amino-aciduria esseva constatate. Studios de controlo subsequente in iste patientes revelava un retorno a valores normal.

Le configurationes chromatographic de amino-acido resimilava strictemente illos reportate in injuria hepatic in que le amino-acidos a contento de sulfure esseva marcatemente augmentate. Iste observation pare supportar le concepto de un mechanismo renal de "effluxo per surabundantia" pro le amino-aciduria. Le recentemente describite capacitate de salicylatos de blocar le production de phosphato a alte energia es forsan responsabile pro le non-incorporation del excesso de amino-acidos in proteina.

TRIAMCINOLONE IN THE THERAPY OF CHRONIC BRONCHITIS AND PULMONARY EMPHYSEMA

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The magnitude and thus the importance of pulmonary emphysema are underscored by the numerous articles about this distressing disease. As excellent examples, mention might be made of the papers, chiefly on aspects other than therapy, presented at the Aspen Conference[10] in June, 1958, and published in July, 1959, and the one by Richards[8], which was published in December, 1960.

As Richards[8] points out, there appear to be three etiologic types of pulmonary emphysema: 1) that resulting from chronic bronchitis, 2) the form produced by pulmonary fibrosis due to such diseases as pneumoconiosis and tuberculosis, and 3) the atrophic or degenerative type, which is of unknown cause and in which obstruction plays no role as it does in the other two. Infrequently is the problem of causation simple and that of emphysema proves no exception. Richards states, in the article cited, that frequently "these factors may co-exist, one complicating the other, so that in the later stages of an individual case, it may be impossible to determine which was the primary etiologic type."

Of the three etiologic types of emphysema, the major one is probably due to chronic bronchitis. Since pulmonary emphysema *per se*, however, produces obstruction with resultant stasis of bronchial secretions, chronic bronchitis may not only be an etiologic factor in emphysema but, as has been stated, a sequel as well.

The patients who are subjects of this study were thought to be afflicted with chronic bronchitis and emphysema of types 1 and 2, with the chronic bronchitis probably a sequel of the latter type as a result of silicosis. Silicosis, as will be seen, in the patients so afflicted was due to employment in the hard coal mines.

Of all the manifestations of bronchitis and emphysema none is more distressing than dyspnea, particularly when present at rest or on slight exertion. Alleviation of this symptom is a prime objective of therapy. Usually, for patients not in the terminal phase of the emphysematous process, treatment consists chiefly of advice to refrain from cigarette smoking and the administration of bronchodilators and antibiotics.

The purpose of this study was to

determine whether further measurable relief from breathlessness might be achieved if, to initial bronchodilator and antibiotic therapy, an adrenal steroid related chemically to hydrocortisone is added. With this in mind, a small group of patients with chronic bronchitis and pulmonary emphysema was studied chiefly by various pulmonary function tests. The steroid administered to supplement the bronchodilator-antibiotic therapy was triamcinolone*, which is a hydroxy derivative of prednisolone containing a fluoride atom. In the discussion section of this paper a comparison between our study and those of a similar nature will be made.

TABLE 1.—AGE DISTRIBUTION OF PATIENTS WITH CHRONIC BRONCHITIS AND PULMONARY EMPHYSEMA

Age	*No. of Patients*
50–59	3
60–69	12
70–79	2
TOTAL	17

Materials and Methods. PATIENTS. A total of 17 patients with chronic bronchitis, all considered initially to have an acute exacerbation of this condition, and pulmonary emphysema were the subjects of this study. All were selected on the basis of a favorable clinical response to preliminary antibiotic-bronchodilator therapy in that the acute exacerbation of the bronchitis had been relieved prior to the performance of the pulmonary function tests. Patients who did not respond to antibiotic-bronchodilator therapy and were then given steroids for relief of symptoms were excluded from this study. All 17 patients were males and their age distribution is seen on Table 1. Their smoking habits were not interfered with.

The diagnosis of bronchitis and pulmonary emphysema was established by clinical data and by roentgenographic and ventilatory studies. In all patients symptoms of diminished exercise tolerance were present for at least several years. In all but 2 patients there was physical evidence of an increase in the anteroposterior diameter of the chest, hyperresonance, diminished breath sounds, and expiratory wheezes. In the same number, that is, 15 of the 17 patients the diagnosis of emphysema was confirmed by roentgenographic evidence of hyperaerated lung fields and depressed leaves of the diaphragm. In all patients the diagnosis of chronic bronchitis and emphysema was substantiated by impaired ventilatory studies.

Of the 17 patients, there were 11 with radiologic evidence of silicosis, all having worked for 5 or more years in the hard coal mines of Northeastern Pennsylvania.

METHODS. All 17 patients had ventilatory studies and arterial blood determinations. The former studies were as follows: Untimed capacity, 1 and 3-second timed vital capacities, and maximum breathing capacity. These were measured with a 13.5 L. Collins respirometer. The observed values were calculated as percentages of the predicted values. The predicted timed vital capacity values were those of Gaensler[4]. The predicted values for untimed vital capacity and maximum breathing capacity were calculated from height, weight, age and sex of the patients (Motley, Lang and Gordon[6]). Also determined was the minute ventilation at rest by use of a 120 L. Tissot respirometer.

Arterial blood was collected by an indwelling Cournand needle from the brachial artery, with the patients first at rest and then immediately after exercise. The exercise consisted of climbing up and down a stool 8" high 30 times for one minute. The arterial blood oxygen and carbon dioxide content were determined by manometric Van Slyke appartus and the percentage oxygen saturation was calculated from the oxygen content and oxygen capacity, also measured by the Van Slyke apparatus. The pH was determined in a Cambridge research model pH meter; correction was made to 37° C. according to Rosenthal's equation[9]. Plasma carbon dioxide content was determined from whole blood carbon dioxide content, pH, hematocrit and the normogram of Van Slyke. Carbon dioxide tension was calculated by use of the Henderson-Hasselbach equation.

The pulmonary function studies were done twice on each patient, before and during steroid therapy. After admission to the hospital, all patients were treated for about one

*Triamcinolone, its trade name Kenacort, was graciously supplied for this study by E. R. Squibb and Sons, New York, New York.

week with either intramuscular penicillin 600,000 units daily, or oral tetracycline 250 mg. four times daily. For 3 to 8 weeks they were also given orally ephedrine 24.0 mg. four times daily and phenobarbital 16.0 mg. four times daily. Aminophylline suppositories and isoproterenol hydrochloride by aerosol were also given for varying periods of time.

When the patients, after 3 to 8 weeks of such therapy, had considerably improved from a clinical standpoint as shown by evident decrease in dyspnea and wheezing, the initial pulmonary function studies were done. Then, with the administration of bronchodilators continued, triamcinolone 4 mg. orally every 8 hours for a total of 12 mg. daily, was added to the therapy. The patients received all drugs, including the steroid, for periods ranging from 4 to 8 weeks. Then the pulmonary function studies were repeated. Subsequently, the course of each patient was followed for an additional 1 to 4 weeks, during which time the administration of triamcinolone was tapered off.

Chest roentgenograms, urinalyses, complete blood counts, and 24-hour sputum specimens examined by smear and culture for acid fast bacilli were done during the first few days of hospitalization and repeated monthly during the entire period of observation: from admission to 1 to 4 weeks after completion of the second set of pulmonary function studies. The total period of observation of the patients ranged between 8 and 20 weeks.

OBSERVATIONS. *Other Diseases.* Of the 17 patients with chronic bronchitis and pulmonary emphysema, there were a number with various other diseases as noted in Table 2. The 11 patients with silicosis have already been mentioned.

The 3 patients with cirrhosis were diagnosed on the basis of a history of chronic alcoholism, hepatomegaly, and abnormal BSP determinations. They had no evidence of jaundice or ascites. The patient with cor pulmonale had been successfully treated for cardiac failure; at the time the two sets of pulmonary function studies were done he had no evidence of failure. The patient with luetic heart disease manifested no evidence of congestive heart failure.

Complications During Therapy. During the triamcinolone therapy, 2 patients suffered complications: one developed a rightsided pneumonia and the second polycythemia, the highest hemoglobin and hematocrit being 18.0 gm. and 59.9 respectively. It was believed that these complications were not related to the steroid therapy and treatment with bronchodilators and steroids was not stopped. The patient with pneumonia showed resolution of this process due to antibiotic therapy and when the second set of pulmonary functon studies was done he had no evidence of this complication. The patient with polycythemia remained polycythemic after the steroid therapy was abandoned.

TABLE 2.—OTHER DISEASES IN 17 PATIENTS WITH CHRONIC BRONCHITIS AND EMPHYSEMA

Disease	*No. of Patients*
Silicosis	11
(a) Simple — 4	
(b) Conglomerate — 7	
Laennec's Cirrhosis	3
Essential Hypertension	1
Cor Pulmonale with Failure	1
Syphilitic Heart Disease	1

Laboratory Studies Other Than Pulmonary Function Studies. During the entire period of observation, which ranged from 8 to 20 weeks, chest roentgenograms, except for that of the patient with pneumonia, showed no change. The absence of change included the 11 patients with silicosis, simple and conglomerate. In the roentgenograms of the 7 patients with conglomerate disease, it should be noted there was no evidence of breakdown or cavitation in the conglomerate masses. The sputum examinations for acid-fast bacilli by smear and culture which were negative before triamcinolone therapy remained so during the entire period of observation. Except for the

patient who developed polycythemia, the complete blood count remained essentially unchanged during the period of observation. Urinalyses, essentially normal before therapy, remained so during the entire period of observation.

decreased in 7 patients, the average decrease being 12%; and in the remaining 3 patients, there was no appreciable change. The 1 and 3-second vital capacities were decreased in all patients before triamcinolone therapy and they did not change significantly with

TABLE 3.—VENTILATORY STUDIES BEFORE AND DURING TRIAMCINOLONE THERAPY

Patient	Age (Years)	VC (% of pred.)		1 sec. VC (% of UVC)		3 sec. VC (% of UVC)		MBC (% of pred.)		Vent. L/M	
		BT	DT	BT	DT	BT	DT	BT	DT	BT	DT
1	65	62.0	57.0	55.0	48.0	79.0	72.0	54.4	23.2	9.5	12.6
2	58	63.0		48.0		72.0		30.0		8.6	7.6
3	62	43.0	48.0	34.0	36.0	81.0	73.0	23.0	12.0	7.7	9.9
4	60	45.0		41.0		75.0		12.0		10.3	8.9
5	66	72.0	81.0	29.0	31.0	63.0	58.0	28.0	30.0	11.2	9.4
6	50	71.0	73.0	53.0	45.0	83 0	62.0	45.0	32.0	15.6	8.3
7	68	84.0	79.0	38.0	38.0	89.0	89.0	49.0	23.0	11.6	12.6
8	69	37.6	58.9	58.0	40.0	100.0	82.0	29.0	45.0	10.8	11.3
9	62	43.0	60.0	80.1	40.6	100.0	86.0	27.0	27.0	10.7	11.2
10	70	44.0	36.0	17.0	54.0	77.0	85.0	27.0	19.0	10.6	11.2
11	60	44.0	38.0	22.0	61.0	73.0	85.0	31.0	18.0	10.7	11.9
12	69	66.0	44.0	60.0	60.0	85.0	83.0	29.8	35.0	14.1	10.5
13	70	66.0	68.0	50.0	53.0	85.0	87.0	41.0	46.0	11.7	12.6
14	64	70.0		76.0		92.0		47.0		12.1	11.7
15	51	65.0	62.0	58.0	42.0	81.0	70.0	22.5	26.0	11.7	11.7
16	64	66.0	68.0	64.0	61.0	95.0	93.0	26.0	45.0	12.2	13.4
17	66	69.0	34.0	49.0	46.0	80.0	72.0	26.0	19.0	11.6	12.6

BT—Before Triamcinolone Therapy
DT—During Triamcinolone Therapy
VC—Vital Capacity
MBC—Maximum Breathing Capacity
UVC—Untimed Vital Capacity
Vent. L/M—Ventilation in L. per minute at rest

Normal Values:
VC (% of pred.) —75 or more
1 sec. VC (% of UVC)—83
3 sec. VC (% of UVC)—95
MBC (% of pred.) —75 or more
Vent. L/M — 6.0

Pulmonary Function. From a subjective standpoint, most of the patients experienced additional relief on triamcinolone therapy. They had less exertional dyspnea and noted decrease in cough and expectoration.

The following represents a brief summary of the data listed in Table 3. This indicates little or no objective improvement in the ventilatory tests. The vital capacity of the 17 patients was diminished prior to triamcinolone therapy. With triamcinolone 7 patients increased their vital capacity, the average increase being 8.4%; the vital capacity

steroid treatment. The maximum breathing capacity in all patients impaired before steroid therapy, increased in only 6 patients after they received triamcinolone, the average increase being 4.7%. In only 3 patients did both vital capacity and maximum breathing capacity increase as a result of steroid therapy and in none of these was there an appreciable change in the arterial blood gases (Table 4). All 17 patients hyperventilated at rest before triamcinolone and the degree of hyperventilation did not change appreciably as a result of therapy with this drug.

All of the data with reference to arterial blood studies is recorded in Table 4. Again as with the ventilatory studies, there was little or no objective improvement in the arterial blood gases and pH as a result of steroid therapy. It should be noted that 8 patients did not have complete arterial blood studies.

Prior to steroid therapy, the resting oxygen arterial saturation was 95% or less in all but one patient; in this patient it was 97%. This decreased in 5 patients after such therapy and increased or remained the same in 12 patients. The average arterial saturation before treatment was 87.3 ± 4.5% while the average saturation with triamcinolone was 88.6 ± 2.1%.

TABLE 4.—ARTERIAL BLOOD STUDIES BEFORE AND DURING TRIAMCINOLONE THERAPY

		O_2 sat. (%)		pCO_2 (mm. Hg)		pH	
Patient	*State*	*BT*	*DT*	*BT*	*DT*	*BT*	*DT*
1	R	90.6	94.0	42.0	40.7	7.40	7.41
	E	91.0	88.0	42.0	42.0	7.38	7.38
2	R	78.0	87.0				
	E	75.0	77.0	49.0	50.0	7.39	7.36
3	R	91.0	92.0				
	E	95.0	84.0				
4	R	83.0	81.0				
	E	75.0	85.0				
5	R	78.0	77.0				
	E		77.0				
6	R	89.0	90.0				
	E	93.0	90.0				
7	R	89.0	90.0	34.0	38.0	7.46	7.42
	E	91.0	90.0	30.0	42.0	7.42	7.49
8	R	83.0	84.0	44.0	42.0	7.41	7.41
	E	89.0	89.0	42.0	43.0	7.39	7.38
9	R	89.0	84.0				
	E	94.0	89.0				
10	R	95.0	98.6	41.0	47.0	7.42	7.41
	E	86.0	86.0				
11	R	97.0	92.0	44.0	41.0	7.41	7.41
	E	81.0	81.0	41.0	42.0	7.38	7.39
12	R	90.0	86.0	41.0	42.0		
	E	81.0	78.0	45.0	47.0		
13	R	94.0	94.0	41.0	44.1		
	E	88.0	90.0	41.0	44.1		
14	R	86.0	88.0	40.0			
	E	92.0	89.0	40.0			
15	R	84.0	89.0	35.0	38.0		
	E	76.0	81.0	38.0	40.0		
16	R	86.0	90.0				
	E	90.0	85.0				
17	R	82.0	89.0				
	E	84.0	87.0				

R — Resting
E — Immediately after exercise
BT — Before triamcinolone therapy
DT — During trimacinolone therapy

Normal Values: O_2 sat. (%) (R&E) — 96+
pCO_2 (mm. Hg) (R&E) — 40
pH (R&E) — 7.40

Before steroid therapy, 8 of the 17 patients increased their oxygen saturation after exercise. All of these patients had anthracosilicosis. This response to exercise by miners with silicosis had been noted previously by Motley[5]; it is apparently due to abnormal distribution of air which is improved by hyperventilation associated with exertion.

The changes in the postexercise arterial saturation were unpredictable. However, the average saturation after exercise before steroid therapy was 85.9% and after steroid therapy 85.5%. The pH and pCO_2 did not change significantly with steroids.

Discussion. Review of the literature indicates that there are a number of other terms for the condition called in this paper chronic bronchitis and pulmonary emphysema. The list, probably not complete, is as follows: chronic bronchitis alone, pulmonary emphysema alone, diffuse airway obstruction, and pulmonary emphysema with bronchospasm. This diversity in the nomenclature makes comparative study, therapeutic or otherwise, of this condition somewhat difficult.

In brief, the results of this study of 17 selected patients with chronic bronchitis, in an acutely exacerbated state in which bronchospasm is prominent, and emphysema showed that these patients experienced symptomatic relief by preliminary antibiotic-bronchodilator therapy. With the addition of triamcinolone to this therapy, after clinical improvement was noted, the acutely exacerbated bronchitis terminated, there was additional subjective benefit in many patients, but only insignificant objective or no benefit with regard to the entire group of patients.

Studies similar to ours reported in the literature have revealed conflicting results. Cullen and Reidt[2] administered prednisone daily for one week, gradually reducing the dosage of this drug from 60 mg. to 30 mg. during the period, to patients with diffuse airway obstruction. Their results were similar to ours. They found half the patients to have improved subjectively but found none with significant change in pulmonary function studies. Moyes and Kershaw[7] had a similar experience. They treated 26 patients suffering from chronic bronchitis with 15 mg. of prednisolone daily and tetracycline; a control group of 27 patients was treated with tetracycline and aminophylline. The therapy in both groups was given for 4 months. The results, assessed clinically and by vital capacity determinations, in the two groups were similar, suggesting that steroids have little or no value in the therapy of chronic bronchitis. On the other hand, Franklin and his associates[3] noted not only subjective but also objective benefit in their study. They treated 58 patients suffering from obstructive pulmonary emphysema with bronchodilator drugs and half the cases with corticosteroids as well. They observed with combined therapy an increase in the untimed and 1-second vital capacities, but subjective improvement was greater than that suggested by the objective measurements.

It should be emphasized that this study was not designed to study the immediate effect of steroids plus antibiotics and bronchodilators on patients with chronic bronchitis, acutely exacerbated, and pulmonary emphysema. Those patients who received such therapy to begin with were eliminated from the study. Our own clinical experience with these patients gave information to the effect that frequently such combined therapy will afford either benefit where therapy without steroids may not produce such a result or quicker improvement than steroid-free therapy. That steroid therapy in a similar situation is effective is illus-

trated by two reports. Bickerman and Barach[1] administered ACTH, cortisone, and hydrocortisone to 163 patients with intractable asthma and pulmonary emphysema with bronchospasm. Remission was obtained in the majority of these patients, no matter whether ACTH, cortisone or hydrocortisone was used. Usually they found that patients with bronchial asthma generally manifested a more complete remission than those with bronchospastic type of pulmonary emphysema. Waldman[12] treated a group of 10 patients with intractable asthma, bronchospasm, and pulmonary emphysema with triamcinolone for several weeks. He noted also subjective and objective improvement.

As the incidence of tuberculosis is increased in silicosis, as silicotic conglomerate disease in a large percentage of cases may be due to tuberculosis (Vorwald[11]) and as steroids have been known to exert a deleterious effect on this infection, attention was directed to the roentgenographic and bacteriologic data observed in our patients and particularly to the 11 patients with silicosis. During the period of observation, the 7 patients with conglomerate masses showed no evidence by these findings that the masses had broken down. Whether active tuberculosis would have supervened in these patients, had steroid therapy been continued for long periods of time, cannot be definitely stated. It would be recommended, however, that if prolonged steroid therapy is necessary for one reason or another for a patient with conglomerate disease, antituberculosis chemotherapy should be given in prophylaxis. In none of the other patients did any evidence indicative of pulmonary tuberculosis appear as a result of treatment with steroids.

Summary. Triamcinolone therapy in 17 patients with chronic bronchitis and pulmonary emphysema, who had shown improvement on preliminary antibiotic-bronchodilator therapy, produced insignificant additional or no betterment as indicated by physiologic measurements of pulmonary function.

With this steroid, most of the patients, however, showed subjective improvement which obviously bore no relation to the results of the pulmonary function tests.

Radiologically and bacteriologically, there was no evidence of the development of pulmonary tuberculosis or of breakdown of the conglomerate masses as a result of steroid therapy.

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(Interlingua on page 447)

A MEASURE OF THE EFFECTIVENESS OF PROPOXYPHENE ANTITUSSIVES IN CHILDREN

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A relatively new chemical structure (Pohland and Sullivan[4]) has been studied for analgesic (Gruber[3]) and antitussive (Bickerman *et al.*[1], Gruber *et al.*[2]) action in humans. The cough response of healthy human subjects stimulated by citric acid aerosol (Bickerman *et al.*[1]) was quantitated following oral doses of the hydrochloride salts of dl-propoxyphene, d-propoxyphene, and l-propoxyphene. Suppression of the response occurred with all three. The salt of l-propoxyphene had the greatest potency. Further unpublished studies indicate that l-propoxyphene 2-naphthalene sulfonate and l-propoxyphene oxide hydrochloride are also active.

Clinical study, after the initial demonstration of antitussive activity, continued in patients with acute respiratory tract disease (Gruber *et al.*[2]). This work to be reported in this paper includes two comparisons of blank and propoxyphene antitussives. Although the results of these two studies were obtained at different times and with capsules of different colors, the methodology was the same and they will be reported together.

Methods. The medications included in this study are presented in Table 1. They were prepared in bottles of 28 capsules. Thus, one package was sufficient for 7 days of therapy, 4 capsules per day.

The patients were inmates of a home for children. The capsules were administered for the control of cough associated with acute respiratory tract disease. Since it was probable that no more than 7 days of therapy would be necessary, a report with only one medication could be obtained from each patient. Comparison among groups of children was, therefore, necessary in order to compare various preparations. Other medications (for example, antipyretic analgesics, antibiotics, and others) were given as necessary for proper patient care.

The effectiveness of the drugs was evaluated 3 to 5 days after therapy was started. The questions selected for the evaluation of cough relief, the empirical scales used to quantitate the response, and the scores arbitrarily assigned to these scales are presented in Table 1.

Since there were 22 patients in each group, 22 reports were obtained with each medication. The data were subjected to statistical analysis in accordance with methods reported in standard textbooks on this subject.

Results. The data are summarized in Table 1 and variance analysis is presented in Table 2. The differences among the responses to the questions, as might be expected, are significant. The medications also were associated with a significant deviation from randomness. The groups of reports with capsules of blank (the connecting link between the two studies) were not significantly different. The least effective drug-dose (l-propoxyphene 2-naphthalene sulfonate, 25 mg.) was

associated with significantly lower cough and expectoration scores than were obtained when the blank was given. The responses to all of the other medications, therefore, were also statistically significant.

The interaction between question and medication was also statistically significant. The previous report (Gruber *et al.*[2]) suggested, but did not establish, a disparity between suppression of cough and suppression of expectoration when 1-propoxyphene oxide was administered. Such an effect would

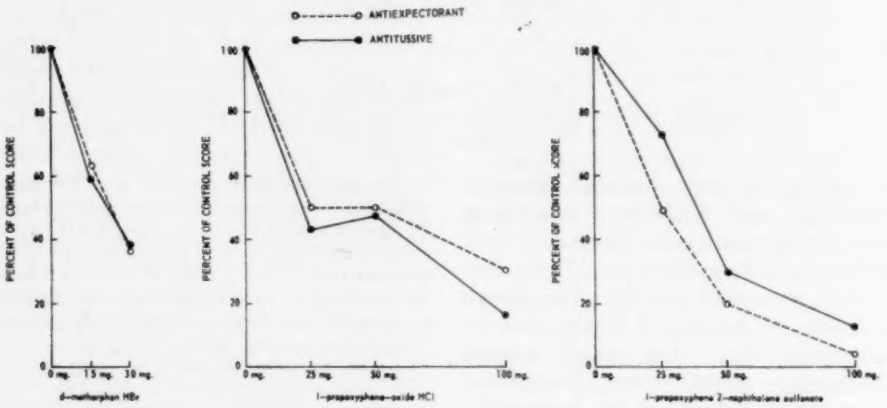

Fig. 1.—The antiexpectorant and antitussive actions of the drugs.

TABLE 1.—A SUMMARY OF THE DATA OBTAINED USING THE EMPIRICAL SCALES AND ARBITRARILY ASSIGNED SCORES. THE BODY OF THE TABLE PRESENTS THE TOTAL SCORES OBTAINED FROM THE 22 PATIENTS ADMINISTERED EACH MEDICATION. THE QUESTIONS I, II, III, IV, and V ARE PRESENTED BELOW

Medication	*Dose in mg.*	*I*	*II*	*III*	*IV*	V
d-Methorphan Hydrobromide	15	33	36	36	23	30
d-Methorphan Hydrobromide	30	21	24	24	12	19
1-Propoxyphene Oxide Hydrochloride	25	28	28	22	22	23
1-Propoxyphene Oxide Hydrochloride	50	27	29	29	17	24
1-Propoxyphene Oxide Hydrochloride	100	12	9	9	7	14
Blank 1 (Cornstarch)		55	60	62	42	41
Blank 2 (Cornstarch)		68	73	69	45	41
1-Propoxyphene 2-Naphthalene Sulfonate	25	51	50	53	21	22
1-Propoxyphene 2-Naphthalene Sulfonate	50	21	23	26	9	9
1-Propoxyphene 2-Naphthalene Sulfonate	100	9	10	10	2	3

I. How much did your cough bother you while you were taking your medicine? _____
(0) none (1) a little (2) some (3) a lot (4) terribly

II. How often did you cough while taking your medication? _____
(0) none (1) occasionally (2) sometimes (3) frequently (4) all of the time

III. How hard did you cough while taking your medication? _____
(0) none (1) hacking (2) single coughs (3) multiple coughs (4) loss of breath

IV. How often did you bring up something when you coughed? _____
(0) never (1) rarely (2) half the time (3) usually (4) all of the time

V. What is the most that you have brought up? _____
(1) a little (2) some (3) a lot

contribute to the significance of the interaction term. Figure 1 expresses the antitussive and antiexpectorant actions of these drugs. The magnitude of the difference is presented in Fig. 2. Significantly less antiexpectorant action was observed with l-propoxyphene oxide and significantly more was reported when l-propoxyphene 2-naphthalene sulfonate was given.

Discussion. Two therapeutic actions are usually of value in treating cough. The first is the suppression of cough so as to minimize the disturbance this symptom causes the patient. However, cough is a protective phenomenon and frequently is desirable as a means of removal of material from the respiratory tract. Therefore, complete suppression may be unwanted.

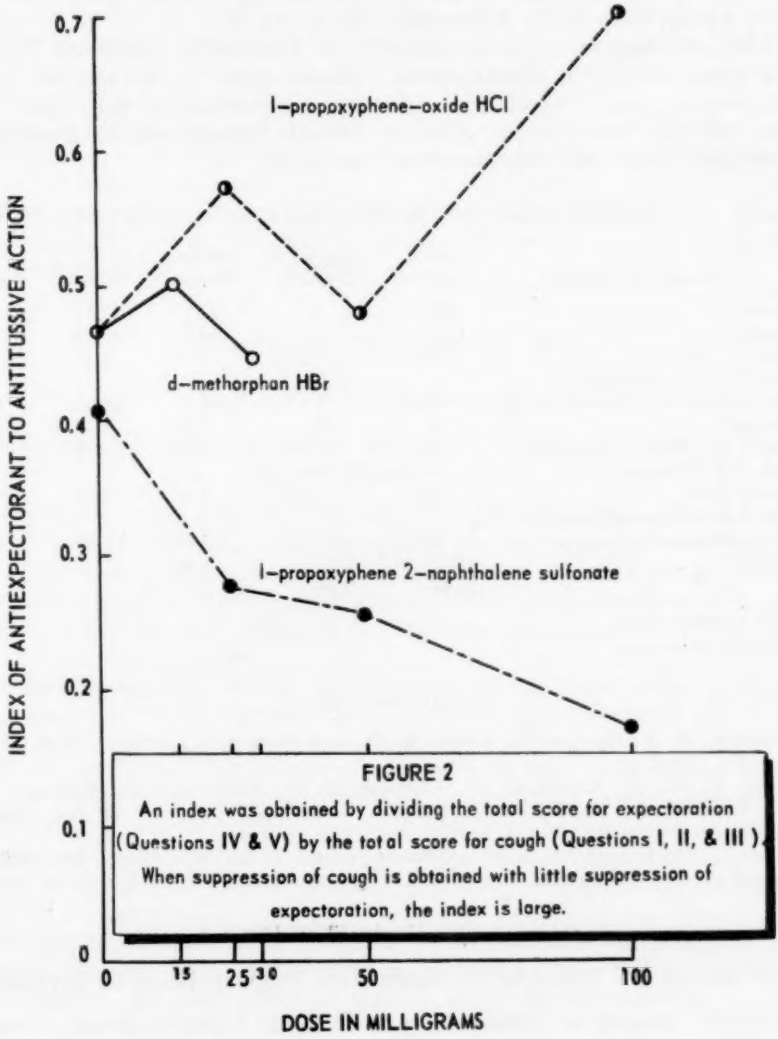

FIGURE 2

An index was obtained by dividing the total score for expectoration (Questions IV & V) by the total score for cough (Questions I, II, & III). When suppression of cough is obtained with little suppression of expectoration, the index is large.

Fig. 2

The second therapeutic action of a cough preparation is thinning or liquefication of sputum. This action facilitates the removal of material from the respiratory tract. Thus, ineffective coughs are less apt to occur.

The medications which are prescribed usually have both actions. Therefore, nearly all of the preparations in use are mixtures of drugs. It is of interest, therefore, that one chemical, 1-propoxyphene oxide hydrochloride, has been shown to suppress cough to the same extent as d-methorphan and 1-propoxyphene 2-napthalene sulfonate, but does not have as great a suppressant effect on expectoration. For a single chemical to be antitussive and expectorant is unique. The clinical importance of this finding is, however, not established since mixtures of drugs can perform both actions simultaneously.

Conclusions. 1. Patients administered 1-propoxyphene oxide hydrochloride or 1-propoxyphene 2-naphthalene sulfonate in equal milligram doses reported approximately the same relief from cough.

2. Patients administered 1-propoxyphene oxide hydrochloride reported more expectoration than those administered 1-propoxyphene 2-naphthalene sulfonate.

TABLE 2.—VARIANCE ANALYSIS OF THE DATA SUMMARIZED IN TABLE 1

Source of Variance	*Sum of Squares*	*Degrees of Freedom*	*Mean Square*	*F Value*	*p Less Than*
Questions	84	4	21.0	15.11	0.001
Medications	601	9	66.8	42.82	0.001
Blank 1 vs. Blank 2	(5.9)	(1)	5.9	1.45	
Blank 2 vs. 1-Propoxyphene 2-Naphthalene Sulfonae, 25 mg.	(44.6)	(1)	44.6	32.05	0.001
Interaction*	56	36	1.56	2.33	0.01
Blank 1 vs. d-Methorphan HBr	3.28	(1)	3.28	4.89	0.05
Blank 1 vs. 1-Propoxyphene Oxide HCl	4.00	(1)	4.00	5.94	0.05
Blank 2 vs. 1-Propoxyphene 2-naphthalene Sulfonate	7.89	(1)	7.89	11.80	0.001
Remainder**	707	1050	0.67		
Total	1448	1099			

* Error for main effect

** Error for interaction

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SUMMARIO IN INTERLINGUA

Un Mesura del Efficacia de Antitussivos Propoxyphenic in Juveniles

1. Patientes tractate con hydrochloruro de oxydo 1-propoxyphenic o con sulfonato 1-propoxypheno-2-naphthalenic in doses equal in milligrammas reportava approximativemente le mesme alleviamento de tusse.

2. Patientes tractate con hydrochloruro de oxydo 1-propoxyphenic reportava plus expectoration que patientes tractate con sulfonato 1-propoxypheno-2-naphthalenic.

SUMMARIO IN INTERLINGUA

(See page 436 for original article)

Triamcinolona in le Therapia de Bronchitis Chronic e de Emphysema Pulmonar

Therapia a triamcinolona, usate in 17 patientes con bronchitis chronic e emphysema pulmonar qui habeva monstrate varie grados de melioration sub le effecto de un therapia antibiotico-bronchodilatatori preliminari, produceva insignificative o nulle melioration additional a judicar per mesurationes physiologic del function pulmonar.

Tamen, con le uso del steroide, le majoritate del patientes monstrava melioration subjective, le qual—obviemente—habeva nulle relation con le resultatos del tests de function pulmonar.

Studios radiologic e bacteriologic monstrava nulle indication de un disvelloppamento de tuberculosis pulmonar o de un collapso del massas conglomerate como resultato del therapia a steroide.

SUMMARIO IN INTERLINGUA

(See page 475 for original article)

Metabolismo de Hydrato de Carbon in Normal Vetulos e Vetulas de Plus Que Septanta Annos de Etate

1. Studios de chimia de sanguine del typos tendente a revelar le existentia de un defecto in le metabolismo de hydrato de carbon esseva effectuate in 49 "normal" vetulos e vetulas de plus que 70 annos de etate. Iste tests includeva un proba standard del tolerantia pro glucosa oral e determinationes in stato jejun del acido lactic, del acido citric, e del fractiones phosphatic a solubilitate per acido organic in le sanguine.

2. Quaranta-duo del probas de tolerantia pro glucosa esseva completate. Omnes esseva anormal, representante variationes inter un curva minimemente diabetic e un curva moderatemente diabetic.

3. Nulle significative differentias poteva esser detegite in le valores sanguinee de acido lactic, acido citric, e fractiones phosphatic a solubilitate per acido organic inter, de un latere, le gruppo del vetulos e vetulas e, del altere latere, duo gruppos de controlo de plus juvene subjectos, le un consistente de personas con normal curvas de tolerantia pro glucosa e le altere de personas con levemente elevate tal curvas.

4. Remaneva inconclusive le essayo de establir un correlation inter le valores sanguinee de acido lactic, acido citric, e fractiones phosphatic a solubilitate in acido organic e, del altere latere, le typo de curva diabetic obtenite.

THE EFFECT OF PROBENECID AND OF LIVER DISEASE ON THE EXCRETION OF PHENOLSULFONPHTHALEIN

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The initial intent of the present investigation was a clinical determination of the degree of inhibition of phenolsulfonphthalein (P.S.P.) excretion by various doses of probenecid. Beyer *et al.*[4] demonstrated that probenecid (p-[di-n-propylsulfamyl] benzoic acid) inhibits the renal excretion of P.S.P. It is more potent in its effect on the renal tubules than the related drug, caronamide. In human studies caronamide reduces the excretion of P.S.P. when it is given in relatively large intravenous doses, but not when given orally (Boger and Crosson[7]). Only one experiment has been published in which the inhibitory effect of probenecid on the excretion of P.S.P. has been demonstrated in man (Boger and Smith[9]). During the course of the present study, it was observed that the response to probenecid of some patients with liver disease differed from that of all other individuals tested. Therefore, an attempt was made to elucidate this unexpected finding.

Material and Methods. All 67 subjects were men hospitalized in the Pittsburgh V.A. Hospital. The 30 "normals" were hospitalized for minor surgical or psychiatric complaints. The second group consisted of 10 patients who were receiving 20 mg. of Prednisone per day. Seven of these had rheumatoid arthritis and 3 had rheumatic fever without apparent cardiac involvement. The 27 patients in the liver disease group consisted of 23 men with Laennec's cirrhosis, 1 with chlorpromazine hepatitis and 3 with extrahepatic obstructive jaundice. Cirrhosis was proven by biopsy in 7 cases and by necropsy in 3. The hepatitis was proven by biopsy and the obstructive jaundice was demonstrated at surgery to be due to carcinoma of the head of the pancreas with no hepatic abnormality other than bile stasis. To be included in the liver disease group a patient had to have ascites, jaundice, or if neither of these signs were present, a history of alcoholism and bromsulphalein dye retention of at least 20% in 45 minutes.

Every subject drank about 800 ml. water and 30 minutes later received 1 ml. (6 mg.) of P.S.P. intravenously. Urine was collected 30 minutes thereafter. Probenecid was then given orally, and the P.S.P. test was repeated 6 hours and 24 hours later. Patients were not catheterized, but none had symptoms of urinary obstruction. Every specimen was larger than 60 ml. The series of liver disease cases was not consecutive because several patients with ascites were unable to void at the specified times and, therefore, had to be eliminated from the study.

Results. Tables 1 and 2 show that in men who do not have liver disease probenecid regularly inhibits the renal excretion of P.S.P. The effect is related to the dose of probenecid used. One half gram of probenecid 6 hours after it has been ingested exerts a slight but statistically significant effect on P.S.P. excretion. The effect of 1.5 gm. is more pronounced, and the effect of 3.0 gm. is still greater. The concurrent chronic administration of Prednisone does not alter the effect of probenecid. In all control cases in whom 1.5 gm. or 3.0 gm. of probenecid was given, the excretion of P.S.P. in the test done 6 hours after the ingestion of probenecid was at least 10% less than the control value. Twenty-four hours after 1.5 gm. of probenecid have been ingested the effect has worn off. A sig-

nificant effect remained 24 hours after 3.0 gm. had been ingested.

In 10 tests of 9 cirrhotic patients the excretion of P.S.P. actually was greater 6 hours after probenecid had been ingested than in the control tests. In 20 tests on 16 patients with hepatocellular disease, the quantity of P.S.P. excreted

P.S.P. excretion following probenecid ingestion, together with the simultaneous serum bilirubin concentrations of the 9 patients with hepatocellular disease who were tested twice. These responses are representative of those encountered in the entire liver disease group. They indicate the randomness

TABLE 1.—EFFECT OF PROBENECID ON EXCRETION OF P.S.P.

Group	*Subjects*	*Ave. age*	*Dose of probenecid*	*Control % excretion*	*6 hours % excretion*	*24 hours % excretion*	*Control vs. 6 hours*
Normal	10	43.1	0.5 gm.	59.6 ± 9.90	50.4 ±11.09		$p<0.01$
Normal	10	43.3	1.5 gm.	57.0 ± 7.53	37.1 ± 8.08	53.0 ± 4.54	$p<0.01$
Normal	10	39.7	3.0 gm.	59.3 ±12.06	30.6 ± 9.04	46.5 ±10.42	$p<0.01$
Prednisone	10	42.5	1.5 gm.	54.2 ±13.06	32.2 ±11.43	51.2 ±12.34	$p<0.01$

TABLE 2.—REDUCTION OF P.S.P. EXCRETION 6 HOURS AFTER INGESTING PROBENECID. (NORMAL DEFINED AS 15% TO 30% LESS THAN CONTROL.)

				Response		
Group	*Dose*	*Tests*	*Serum bilirubin*	*Normal*	*<−15%*	*>−30%*
Normal	0.5	10		0	100%	0
Normal	1.5	10		80%	10%	10%
Normal	3.0	10		30%	10%	60%
Prednisone	1.5	10		80%	10%	10%
Cirrhosis	1.5	8	<1.5 mg./100 ml.	62.5%	25%	12.5%
Cirrhosis	1.5	6	1.9– 3.0 mg./100 ml.	0	67%	33%
Cirrhosis	1.5	19	3.2–27.0 mg./100 ml.	31.5%	58%	10.5%
Obstructive	1.5	3	19 –23 mg./100 ml.	0	67%	33%

6 hours after the ingestion of probenecid was less than 15% below the control value. Two patients with jaudice due to extrahepatic obstruction also had a subnormal response to probenecid. Of the 20 control subjects who were tested with 1.5 gm. of probenecid the 24 hours test value differed from the pre-drug test result by 10% or more only 3 times. This occurred 11 times in 33 tests in hepatocellular disease and in 1 of the 3 cases of obstructive jaundice.

Table 3 presents the changes of

of the response to probenecid that was often observed in the presence of severe liver dysfunction.

Our data support the view that excretion of P.S.P. tends to be greater than normal in the presence of liver disease when overt renal disease is absent. Fourteen of the 27 patients in the liver disease group excreted at least 70% of P.S.P. in at least one 30-minute specimen (52%), while only 5 of 40 control subjects did this (12.5%). At least 70% of the dye was excreted in 30 minutes in 22% of the 108 tests done

on liver disease patients. This occurred in only 6% of 120 tests done on the control subjects.

The urine flow during the P.S.P. tests was greater in the control subjects than in the patients with cirrhosis or with than the two morning specimens in all groups. These data are presented in Table 4.

Discussion. The smaller volume of the specimens of the patients with diseases affecting the liver is attributable

TABLE 3.—THE EFFECT OF 1.5 GM. PROBENECID ON THE EXCRETION OF P.S.P. IN LIVER DISEASE. PATIENT IN WHOM DUPLICATE TESTS WERE PERFORMED.

Patient	*Age*	*Serum bilirubin*	*Excretion Control vs. 6 H.*	*Excretion Control vs. 24 H.*	*Days between*
V.S.	45	19.6	+ 6%	+ 1.5%	
		8.8	−14%	− 7.5%	17
P.W.	36	14.6	−29%	0	
		10.9	−54.5%	− 6%	21
W.L.	35	12.4	−14.5%	− 3.5%	
		7.3*	+26%	+15%	55
L.F.	38	10.0	+ 3%	+ 4%	
		9.3	−21.5%	− 2.5%	19
A.S.	43	9.0	+14%	+40%	
		2.2	+14.5%	+43.5%	32
V.Z.	46	5.7	−22%	−10%	
		0.7	−20%	− 9%	17
J.R.	†25	5.2	+ 9%	+ 4%	
		1.0	− 9%	−10%	14
T.S.	47	3.0	+ 9%	0	
		4.1	−20%	+ 2.5%	82
H.L.	38	2.9	+20%	− 3%	
		1.0	−26%	−20%	13

†Chlorpromazine hepatitis, portal fibrosis. All other cases Laennec's cirrhosis.
*Died of hepatic failure 15 days after test performed.

TABLE 4.—URINE FLOW DURING P.S.P. TESTS, IN ML. PER MINUTE.

Group	*Tests*	*Control*	*6 hours*	*24 hours*
Control	30	10.1 ± 6.44	16.8 ± 6.78	9.1 ±3.52
Cirrhosis Bilirubin < 3.0	14	5.2 ± 3.10	12.9 ± 7.21	7.1 ±3.11
Cirrhosis Bilirubin > 3.1	19	5.4 ± 3.91	9.3 ± 6.65	5.7 ±3.79
Obstructive jaundice	3	6.9 ± 1.40	9.7 ± 1.90	5.6 ±1.41

obstructive jaundice. The mean volumes were not related to the degree of icterus and the urine volumes of the patients with obstructive jaundice were consistent with those of the patients with cirrhosis. The afternoon specimen, which was obtained 6 hours after the ingestion of probenecid, was larger to the increase of antidiuretic hormones which occurs in such diseases. Probenecid does not affect the glomerular filtration rate (Baer *et al.*[1]). Therefore, the observation that the volume of the afternoon specimens usually was greater than the volume of the morning specimens cannot be attributed to an

effect of this drug. Larger afternoon urine volumes were obtained irrespective of the presence of liver disease or degree of jaundice. This supports the view that the manner in which many of the jaundiced patients responded to probenecid was not due to an alteration of the urine flow in these individuals in comparison to those who reacted "normally." The large afternoon volumes are best explained by better hydration at that time.

Two mechanisms have been proposed to explain the retarding effect of probenecid on renal excretion: 1) Probenecid may retard the excretion of some substances which are poorly excreted without being conjugated by interfering with conjugative mechanisms (Beyer *et al.*[5], Boger, Pitts and Flippin[8]). It is doubtful whether such an effect is of importance. 2) Probenecid may exert a competitively inhibitory effect on a renal tubular secretory mechanism (Weiner, Washington and Mudge[22]).

Probenecid has been shown to retard the renal excretion of ACTH (Bonar and Perkins[10]), androsterone (Bongiovanni and Eberlein[11]), estrogen (Gardner, Crigler and Migeon[13]), pantothenic acid (Boger *et al.*[6]), penicillin (Boger, Pitts and Flippin[8], Crosley *et al.*[12]), sulfonamides (Crosley *et al.*[12]), salicylic acid (Weiner, Washington and Mudge[21]), p-amino salicylic acid (Boger, Pitts and Flippin[8]), p-amino hippuric acid (Beyer *et al.*[4]), acetazolamide (Weiner, Washington and Mudge[21]), chlorothiazide (Baer *et al.*[1]), Diodrast (Beyer *et al.*[4]) and P.S.P. (Beyer *et al.*[4], Boger and Smith[9]). A common tubular excretory mechanism has been postulated for these substances, mainly because of the similar effect probenecid exerts on their excretion.

Probenecid *in vitro* reduces the conjugation with glycine of p-amino benzoic acid and of p-amino salicylic acid (Beyer[3]). Since p-amino salicylic acid is excreted largely as a glycine conjugate, and its excretion is retarded by probenecid, interference with conjugation may be responsible for this effect (Beyer *et al.*[5]). Acetylsalicylic acid, which is excreted principally as salicyl glucuronide, is not affected by probenecid (Weiner, Washington and Mudge[22]). Probenecid also does not interfere with the acetylation of sulfonamides (Crosley *et al.*[12]). Liver failure does not prevent absorption of orally administered probenecid (Benedek[2]).

The greater part of intravenously injected P.S.P. becomes bound to serum albumin (Smith and Smith[19]). It has been assumed that this dye is excreted by the kidneys without being conjugated or otherwise altered. However, there are no data bearing on this.

Thompson, Frazier and Ravdin[20] performed P.S.P. tests on dogs 10 to 88 days after ligation of the common bile duct. The results of these tests were in the normal range, but preoperative data were inadequate to permit evaluation of possible changes in excretion which might have resulted from the progressive jaundice. Hamner and Whipple[14] produced jaundice in dogs by ligation of the common bile duct and also by injuring the liver with chloroform anesthesia. In both types of experiments the urinary excretion of P.S.P. one hour after intravenous injection was greater after liver injury. They concluded that the liver normally excretes 10 to 15% of intravenously administered P.S.P.

Clinical observations have varied. The observations of Patek, Seegal and Bevans[18] support the experimental results of Hamner and Whipple. They investigated 8 patients with chronic glomerulonephritis and cirrhosis whose

plasma nonprotein nitrogen concentration was between 55 mg. per 100 ml. and 130 mg. per 100 ml.; 3 were jaundiced. Excretion of P.S.P. ranged from 25% to 60% in 2 hours. This is greater than would be expected under these circumstances when liver function is normal. However, according to Paris[17] the P.S.P. excretion is normal in cirrhosis when the glomerular filtration rate is normal, and this usually is so (Papper[16]).

Probenecid is excreted in the urine only in severe alkalosis. It normally appears to be continually secreted and reabsorbed by the renal tubules (Weiner, Washington and Mudge[22]). It has been postulated that probenecid, in analogy with caronamide, undergoes conjugation with glucuronide (Boger, Pitts and Flippin[8]). The glucuronide conjugations of bilirubin and of corticosteroids are known to be hepatic functions. It is likely that such conjugation of sulfamyl-benzoic acids, such as probenecid, also takes place in the liver. It may be that probenecid must become conjugated before it exerts its effects on the renal tubules. In severe liver disease this conjugative mechanism may become defective, with the result that little effective probenecid reaches the renal tubules and the tubular mechanism remains available for the excretion of P.S.P.

Summary. The effect of probenecid in single oral doses of 0.5 gm., 1.5 gm. and 3.0 gm. on the urinary excretion of P.S.P. was determined in normal men. Probenecid consistently retarded the excretion of P.S.P., the degree of retardation increasing with the dose of probenecid administered. The effect was identical in patients with normal hepatic function who were receiving Prednisone over long periods. In a significant number of patients with liver disease sufficient to cause jaundice, probenecid had little or no depressant effect on the excretion of P.S.P. This is not due to lack of absorption of probenecid or to altered glomerular filtration in the presence of liver disease.

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SUMMARIO IN INTERLINGUA

Le Effecto de Probenecido e de Morbo Hepatic Super le Excretion de Phenolsulfonphthaleina

Le effecto de probenecido in solitari doses oral de 0,5, 1,5, e 3 g super le excretion urinari de phenolsulfonphthaleina esseva determinate in masculos normal. Esseva trovate uniformemente que probenecido retarda le excretion de phenolsulfonphthaleina e que le grado del retardo cresce con le dose de probenecido administrate. Le effecto esseva identic in patientes con normal functiones hepatic qui recipeva prednisona durante prolongate periodos de tempore. In un numero significative de patientes con morbo hepatic de gravitate sufficiente a causar jalnessa, probenecido habeva pauc o nulle effecto depressive super le excretion de phenolsulfonphthaleina. Isto non es causate per un inadequate absorption de probenecido o un alteration del filtration glomerular in le presentia de morbo hepatic.

SUMMARIO IN INTERLINGUA

(See page 481 for original article)

Sexo e Diabete Mellite: Un Studio Comparative de 26 Masculos Negre con 26 Femininas Negre, Appareate con Respecto al Etate

Vinti-sex non-seligite patientes diabetic mascule esseva appareate individualmente relative al etate con 26 patientes diabetic feminin. Omnes esseva de racia negre. Un studio comparative de iste specimen esseva de racia negre. Un studio comparative de iste specimen esseva executate pro determinar si le subgruppos mascule e feminin differeva significativemente le un ab le altere con respecto al duration del diabete, al grado de obesitate, al methodo de stabilisation, al diagnose cardiac, e al uso facite del dispositivos clinic e hospitalari. Differentias significative inter le gruppos esseva trovate solmente con respecto al obesitate —le femininas esseva significativemente plus obese que le masculos—e con respecto al grado de stabilisation—le masculos revelava un grado de stabilisation significativemente melior que le femininas.

Le constatationes del presente studio se trova de accordo con illos de Duncan[2], Williams[7], e Vinke *et al.*, qui assere que le plus alte incidentia de diabete in femininas de etates de plus que 50 annos es associate con obesitate e que obesitate es un importante factor in le effortio de meliorar le stabilisation del patiente diabetic. Le presente analyse non permitte conclusiones con respecto al causas de iste observationes, sed varie possibilitates es discutite.

THE GASTROINTESTINAL ABSORPTION OF ORAL IRON-DEXTRAN AND FERROUS SULFATE

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New oral iron preparations of varying compositions are constantly being made available for therapeutic use in iron deficiency anemias. Several of these new compounds contain iron in the form of iron-dextran complexes. The rate of gastrointestinal absorption of the iron in the iron-dextran complex is not known. The efficacy of any oral iron preparation will depend upon the rate of gastrointestinal absorption and on the total amount of iron in the preparation. The purpose of this study was to compare the rate of gastrointestinal absorption of an oral iron-dextran complex with the rate of gastrointestinal absorption of ferrous sulfate in the same subjects. Known amounts of the iron compounds labeled with radioactive iron, Fe^{59}, were given orally. The difference between the amount of iron given orally, and the iron recovered in the stools, as measured with a scintillation counter, was assumed to represent the amount of iron absorbed.

The technique utilized for measuring the gastrointestinal absorption of oral iron was similar to that described by Bonnet, Hagedorn and Owen[1] in which small doses of iron were used. With small doses, a larger percentage of oral iron is normally absorbed so that it is possible to detect decreased absorption.

Materials. Fe^{59} as ferrous sulfate solution was prepared so that one microcurie of Fe^{59} was present in 50 μg. of elemental iron. The specific activity of the Fe^{59} in the iron-dextran complex* was lower, so that 354 μg. of elemental iron was present for each microcurie of Fe^{59}. A minimum dose of one microcurie was necessary because of the limited sensitivity of the scintillation detector employed. Therefore, the amount of elemental iron in a single dose of iron-dextran was approximately seven times greater than that present in a single dose of the ferrous sulfate.

Methods. The same methods were utilized for measuring the absorption of both the ferrous sulfate and the iron-dextran complex. The iron solution was measured into a wax drinking cup, and the subjects, in a fasting state, drank the solution, rinsing the cup several times. All subsequent stools were individually collected until a single stool contained less than 1% of the administered dose, usually for 3 or 4 days. The subjects were initially given the ferrous sulfate solution. Two weeks later, which was at least a week after the stools no longer contained significant Fe^{59} from the initial dose, they received the iron-dextran complex.

The activity of the Fe^{59} in the stools was determined by measuring over a well counter. Pilot samples of both iron compounds were prepared containing the same amount of Fe^{59}, one microcurie, as was present in the oral doses. The activity found in the stools of each patient was compared with that of the pilot, that is, of the oral dose. The amount of

*The organic iron-dextran complex, "Jefron," was obtained from the Pitman-Moore Company, Indianapolis, Indiana. It has a molecular weight of 30,000 and contains 45% iron by weight.

iron not present in the stools was assumed to have been absorbed.

Serum iron determination was performed according to the method of Fister[3].

Results. Eight adults, 7 women and one man, all apparently healthy, ingested the ferrous sulfate solution containing one microcurie of Fe_{59} with 50 μg. of elemental iron. Two weeks later, all these subjects, plus one other healthy adult woman, ingested the iron-dextran complex which contained one microcurie of Fe_{59} and 354 μg. of elemental iron. The hemoglobin of the 8 women ranged from 11.6 to 13.5 gm. per 100 ml. of blood. Their serum iron ranged from 50 to 110 μg. per 100 ml. The one man had a hemoglobin of 15 gm. per 100 ml. of blood, and a serum iron of 95 μg. per 100 ml.

TABLE 1.—GASTROINTESTINAL ABSORPTION OF ORAL IRON

	Ferrous Sulfate Absorption (50 μg. oral dose)		*Iron-Dextran Absorption (354 μg. oral dose)*	
Sex	*% of oral dose absorbed*	*Total μg. absorbed*	*% of oral dose absorbed*	*Total μg. absorbed*
F	29	14	49	173
F	34	17	48	171
F	36	18	50	177
F	44	22	37	131
F	65	33	48	172
F	82	41	54	192
F	88	44	78	278
F	—	—	45	160
M	40	20	46	162
Average	52	26	51	180

As shown in Table 1, the range of absorption of the ferrous sulfate was 29% to 88%, with an average of 52%. The absorption of iron in the form of iron-dextran complex ranged from 37% to 78% of the oral dose with an average of 51%.

Four subjects absorbed 7 to 28% (average 16%) more of the oral iron from ferrous sulfate than from iron-dextran complex. The other 4 subjects absorbed from 6 to 20% (average 14%) more of the oral iron when given the iron-dextran complex. However, the absolute amount of iron was 50 μg. in the ferrous sulfate doses, and 354 μg. in the iron-dextran doses. Therefore, the absolute amount of elemental iron absorbed in the ferrous sulfate studies ranged from 14 μg. to 44 μg., with an average of 26 μg., as compared to a range of 131 μg. to 278 μg., with an average of 180 μg. for the iron-dextran complex.

Discussion. The fractional gastrointestinal absorption of oral ferrous sulfate and iron-dextran was essentially the same. The iron-dextran complex contained approximately seven times as much elemental iron as the ferrous sulfate solution. It has been well-documented that the percentage of oral iron absorbed decreases with increasing doses (Bonnet, Hagedorn and Owen[1], Bothwell, Pirzio-Biroli and Finch[2]). Therefore, the amount of iron absorbed from the iron-dextran complex would exceed that from ferrous sulfate, if similar doses are used.

Therapeutic effectiveness of the oral iron-dextran compound was not evaluated. This could be measured clinically by treating patients with iron deficiency

anemias with this compound. It could also be evaluated by measuring the incorporation of the Fe_{59} from the iron-dextran complex into the circulating red cells. Presumably, the transport and utilization of the iron from the iron-dextran complex would be similar to that of the iron from inorganic iron compounds. This assumption was not proved. If it is proved, oral iron-dextran should be an effective therapeutic agent in iron deficiency anemias.

Gastrointestinal side effects of the iron-dextran complex were not evaluated. The great majority of patients tolerate inorganic iron compounds without significant side effects. In these patients the iron-dextran compounds would not offer any advantage.

Summary. 1. The fractional gastrointestinal absorption of oral iron in the form of ferrous sulfate was meassured in 8 healthy subjects, 7 women and one man. The range of absorption of a test dose of 50 μg. ranged from 29% to 88% of an oral dose of 50 μg., with an average of 52%. This represented an actual absorption of 14 μg. to 44 μg., with an average of 26 μg.

2. In the same 8 subjects, plus an additional woman, the absorption of iron from an iron-dextran complex varied from 37% to 78% of an oral dose of 354 μg., seven times the dose of ferrous sulfate. The average absorption was 51%. The actual absorption ranged from 131 μg. to 278 μg., with an average of 180 μg.

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SUMMARIO IN INTERLINGUA

Le Absorption Gastrointestinal del Complexo Ferro-Dextrano e de Sulfato Ferrose post Administration Oral

1. Le absorption fractional, in le vias gastrointestinal, de ferro oral, administrate in le forma de sulfato ferrose, esseva mesurate in 8 subjectos normal, i.e. 7 feminas e 1 masculo. Le procentages de absorption post un dose experimental de 50 μg variava inter 29 e 88. Le procentage medie esseva 52. Isto representava un absorption absolute de 14 a 44 μg, con un valor medie de 26 μg.

2. In le mesme serie de subjectos, augmentate per 1 femina, le absorption de ferro ab un complexo ferro-dextrano variava inter 37 e 78% de un dose oral de 354 μg (i.e., de 7 vices le dose de sulfato ferrose). Le absorption, medie esseva 51%. Le absorption absolute variava inter 131 e 278 μg, con un valor medie de 180 μg.

CARDIAC OUTPUT MEASUREMENT BY EXTERNAL COUNTING OF A RAPIDLY EXCRETED INDICATOR

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Determination of cardiac output by external precordial counting has been described by many authors and has been shown to compare favorably with the Fick method (Huff *et al.*[3], Schreiner, Lovejoy and Yu[10], Seldon, Hickie and George[11], Shackman[12]). The number of determinations which can be done using the previously reported techniques is limited because of long persistence of the tracer in the body. This is disadvantageous due to the relatively large amount of radiation received by the patient, and the effect of the high residual radioactivity on subsequent repetitions of the measurement. The use of a tracer of short physical half-life, as practiced in a few patients by Shackman[12], would lessen these difficulties. The rapid decay rate, however, is a problem, as it is difficult in most areas to have an adequate supply constantly available. Tracers of long physical half-life are in this sense more desirable, and the present study was undertaken to evaluate the applicability of the precordial counting technique using a tracer of short biologic half-life. In this way, both the problems of storage and of excessive radiation to the patient can be overcome.

Materials and Methods. The indicator chosen was I_{128}-labeled Cholografin‡, a compound used in its nonradioactive form for rapid intravenous cholangiography and cholecystography. For purposes of comparison, determinations were carried out with I_{131}-labeled albumin.

A total of 61 studies was done on 36 patients. These studies fell into four categories: 1) determination of the half-time of disappearance of I_{128} Cholografin from the blood stream (11 patients); 2) duplicate determinations of cardiac output with I_{131} albumin (8 patients); 3) duplicate determinations of cardiac output with I_{128} Cholografin (8 patients);

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‡Cholografin is the di-sodium salt of N,N¹-adipyl-bis(3-amino-2:4:6 triiodobenzoic acid), Squibb, sometimes called Iodipamide, Squibb. The authors are indebted to Dr. Paul Numeroff of E. R. Squibb & Sons for calling their attention to this compound, and for provision of that material used during the early phases of this study.

and 4) comparison of duplicate cardiac output determinations using both indicators in random sequence (9 patients).

The patients were selected randomly, and had a variety of disorders, largely disturbances of electrolyte balance. None had clinically significant heart disease. All were studied in the post absorptive state, and remained quietly in bed throughout the study. Repeat cardiac output determinations were done within a period of 10 to 20 minutes.

The technique of measurement of cardiac output was essentially that described by others, summarized by Gorten and Stauffer[2]. The following points are worthy of specific mention: A No. 18 gauge needle was inserted into an antecubital vein and kept patent with a slow infusion of isotonic saline. Thirty to 100 microcuries of I_{131} albumin or I_{131} Cholografin, in volumes of 0.3 to 1.0 ml., were injected rapidly through the indwelling needle with the arm abducted and elevated. In some studies, venous occlusion was effected by means of a tourniquet which was released just prior to injection. This produced sharper deflections of the curve in nearly every case. The scintillation detector consisted of a thallium activated sodium iodide crystal 2 inches in diameter and in depth, coupled optically to a photomultiplier tube and preamplifier. A collimator with a straight bore 25 mm. in diameter and 57 mm. in length (half-value angle approximately 23°) was used and placed over the 4th rib at the left sternal border with the axis angled slightly toward the apex. The detector output was fed to a count-rate-meter (Nuclear-Chicago Model 1620A) and recorded on a Bristol 0-10 mV. potentiometer recorder with 500 millisecond response time. For the primary circulation chart speeds of 10 inches per minute were generally used with rate-meter time constants of 0.5 to 2.0 seconds and full scale deflection sensitivities of 30,000 to 100,000 cpm. Base-lines and plateaus at "equilibrium" (usually 10 minutes) were recorded using 10 second time constants, the detector-patient relationship having been scrupulously maintained. Blood samples were obtained simultaneously with the plateau recording and blood samples and standards were counted to an error of 3% or less (Loevinger and Berman[6]) using a scintillation well counter and scaler. To estimate the half-life of Cholografin in the blood stream, 11 patients were given 10 to 40 microcuries of I_{131} Cholografin I.V. Blood samples were drawn at 10 minutes and at ½, 1, 3, 6 and 12 hours. The measured radioactivity was graphically plotted against time, and the biologic half-life in blood taken from the smoothed resultant line as the time required for the radioactivity to fall to 50% of the 10-minute level.

CALCULATIONS. Calculation of cardiac output was done in the manner described by Lammerant[5]: $H/S \times F \times BV \times 60 =$ C.O. (L./min.) where H = height of plateau after mixing of the tracer substance in the blood stream (at the time of blood sampling). S = area under the curve inscribed during the first passage of tracer through the heart. (Curves were replotted on semi-log paper and the exponential fall-offs extrapolated to baseline levels for calculation of areas.) F = factor for conversion of inches of chart speed to time. BV = the blood volume or "apparent" B.V. The term "*apparent*" B.V. is used to describe a virtual volume calculated when using Cholografin as the tracer. The factor 60 is used to convert output in seconds to output in minutes.

Results. CARDIAC OUTPUT DETERMINATIONS. Table 1 shows duplicate cardiac index determinations done on three groups of patients. In group 1 with 8 patients on whom duplicate albumin output determinations were done, the percent deviation of a single determination from the mean of the pair varied from ±0.4 to ± 8% and the S.D. of these differences was ±3.24%. The second group, the I_{131} Cholografin series, also showed a high degree of reproducibility in 8 patients, with variations from the mean of from ±0.6% to ±5.7% and a S.D. of ±3.47%. In 9 patients on whom an albumin cardiac output determination was followed by one done with Cholografin (or in the reverse order) the results were similar to the two previous groups. Percent deviation from the mean varied between ±1.6% and ±5.4% with a S.D. of ±3.91%.

BIOLOGICAL HALF-LIFE. The time course of disappearance of tracer amounts of I_{131} Cholografin from the blood was sufficiently variable that we have found no reliable means of computing a "true" blood volume from it. Its biological half-life in 11 patients ranged from 2.25 to 9.0 hours, with a mean of 5.34 hours.

TABLE 1.

Patient	Cardiac Index L./Min./M²	± % Dev. From Mean	S.D. %
DUPLICATE I_{131} ALBUMIN DETERMINATIONS			
D.D	3.30		
	3.25	0.8	
N.K.	4.15		
	3.95	2.5	
V.D.	4.50		
	4.42	0.8	
M.A.	2.86		
	2.84	0.4	±3.24
P.B.	2.90		
	3.40	8.0	
R.D.	6.32		
	6.20	1.0	
A.M.	3.66		
	3.48	2.5	
B.J.	4.40		
	4.20	2.3	
DUPLICATE I_{131} CHOLOGRAFIN DETERMINATIONS			
H.H.	6.32		
	6.35	2.4	
W.T.	4.15		
	3.89	3.2	
M.R.	1.69		
	1.71	0.6	
M.B.	4.07		
	3.63	5.7	±3.47
F.L.	3.82		
	3.94	1.5	
M.G.	3.91		
	4.29	4.6	
V.G.	2.78		
	2.66	2.2	
M.C.	4.33		
	4.68	3.8	
I_{131} ALBUMIN FOLLOWED BY I_{131} CHOLOGRAFIN DETERMINATION			
A.F.	3.40		
	3.35	1.6	
P.V.	2.90		
	2.77	2.3	
B.L.	4.20		
	4.60	4.5	
J.B.	2.47		
	2.60	2.6	
A.I.	5.00		
	5.34	3.3	±3.91
L.W.	4.36		
	4.86	5.4	
A.B.	2.65		
	2.40	4.9	
C.H.	3.52		
	3.79	3.7	
C.M.	4.45		
	4.02	5.0	

RADIATION DOSAGE. Since the radiation delivered by an isotope present within a patient is affected by the time it remains there, we have compared I_{131} Cholografin and I_{131} albumin in this respect. The radiation delivered is directly proportional to the "effective half-life," which is calculated as biological half-life × physical half-life/biological half-life + physical half-life (Beierwaltes, Johnson and Solari[1]). The physical half-life of I_{131} in hours is 193 and the biological half-life of I_{131} albumin is taken as 10.5 days, or 252 hours. I_{131} Cholografin then, with a mean biologic half-life of 5.34 hours, has an effective half-life of 5.20 hours, while that for I_{131} albumin is 109.3 hours. The ratio is 21 to 1.

Discussion. The details of technique, the sources of error, and the advantages of the precordial counting technique for cardiac output measurement have been extensively discussed in the literature and are well summarized by Gorten and Stauffer[2]. The method of calculation employed by us was apparently first proposed by MacIntyre, Pritchard *et al.*[7], who also showed the similarity of the calculation to the classical equation of Kinsman, Moore and Hamilton[4]. Although Shipley *et al.*[13], failed to achieve logical results in the first attempt at a quantitative use of the principle, Veall *et al.*[14], soon published results which were more plausible. Since that time there have been many similar reports.

To evaluate the validity of the method, from these reports we have chosen four (Huff *et al.*[3], Schreiner, Lovejoy and Yu[10], Seldon, Hickie and George[11], Shackman[12]) in which the results were compared to those of the direct Fick in the same individual. Of these duplicates, 107 were made in patients and 22 in dogs. Despite the nonsimultaneous nature of the measurement in some studies, and the variability of cardiac output in anesthetized dogs, we have used all 129 pairs to compute the S.D. of the individual measurements (Fick or radioactive) from the means of the two. This showed an absolute directional deviation of the precordial results of +1.4% from the mean. The standard deviation of the result of either type of measurement from the mean of the two was ±4.7%. Thus the value derived by precordial counting appears to be not significantly different from that obtained by the direct Fick. The validity of a variant in technique, as reported here, may, therefore, be as well tested by comparison with an established precordial method as by comparison with the direct Fick. Since the I_{131} Cholografin results in our hands did not differ significantly from the I_{131} albumin results, its validity would appear to be established.

MacIntyre, Pritchard and Moir[6], were responsible for stating the principle applied in our studies; namely, that the volume BV, or apparent B.V., measured ". . . is not necessarily the circulating blood volume as usually calculated by dilution methods, but is actually the volume of dilution of the injected material at the time when the sample was withdrawn."

Most simply stated, the reason that this "incorrect" BV measurement does not introduce an error is the fact that changes in blood concentration of isotope are reflected not only in blood sample counting, but also in the amount of radioactivity influencing the detector during inscription of the plateau H. The loss of isotope will, therefore, create a "cancellation of errors" effect in that H will decrease by exactly the same proportion that BV increases, with their product remaining unchanged. Thus, any otherwise suitable radioactive material may be used in this manner, provided it meets certain criteria, even though loss of indicator

from the blood be rapid and a true B.V. cannot be measured: 1) It must not be lost *before* reaching the area "seen" by the detector. 2) It must not be lost *into* this area. 3) Enough of it must remain in the circulation long enough to measure "H", and take a blood sample simultaneously, for calculating B.V. or "apparent" B.V.

Since the radiation delivered by any given isotope within the body is proportionate to its $T_{\frac{1}{2}}$, I_{131} Cholografin delivers a radiation dose of about 1/20th that of a similar amount of I_{131} albumin. This means that doses of I_{131} Cholografin may be given which much exceed the permissible amounts of I_{131} albumin and repeatedly given over a period of several weeks if necessary. This greatly extends the usefulness of external detection of radioactive indicators for cardiac output determinations, not only for the reasons above stated, but also because the low remaining "background" counts in the patient simplify technical problems in subsequent determinations. Furthermore, iodine is said to be bound firmly to the Cholografin molecule (Puschel[9]) and, therefore, preparation of the patient with iodine is not necessary. We have confirmed this in our patients, who showed no thyroid uptake of I_{131} after receiving only I_{131} Cholografin. Cholografin normally is excreted 90% in the feces, is not reabsorbed into the enterohepatic circulation, and has the additional advantage of being excreted also by the kidney (Puschel[9]). This occurs to some extent in the presence of normal hepatic function, and will serve as the major excretory pathway in severe hepatic dysfunction, complete excretion occurring in a time nearly comparable to that found with intact hepatic function (Puschel[9]).

Summary. The external precordial counting technique is a well established method of measuring cardiac output. Published reports show an accuracy comparable to the direct Fick. This report describes a modification of the technique which extends its utility.

It is shown that a rapidly excreted radioactive indicator may be used, even though the nature of its disappearance from blood precludes accurate blood volume measurement. Cancelling changes in the equation for calculation of cardiac output make it unnecessary to know the actual blood volume.

The indicator here used, I_{131} Cholografin, was found to have a mean half-time in blood of 5.34 hours. Compared with I_{131} albumin, patient radiation is thus reduced twenty-fold, and more frequent determination can, therefore, be done.

Duplicate determinations of cardiac output using I_{131} Cholografin showed a standard deviation from the mean of 3.91%. This was similar to that found when comparing I_{131} Cholografin with I_{131} albumin (3.47%) and to duplicate I_{131} albumin runs (3.24%). The replicability and magnitude of cardiac output measured with I_{131} Cholografin is, therefore, presumably comparable to the direct Fick, as shown in reports comparing the latter with the precordial counting technique.

ACKNOWLEDGMENT: The authors wish to express their appreciation to Drs. P. Vanamee, H. T. Randall and R. W. Rawson, and Miss Margaret Hood for their advice and assistance.

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SUMMARIO IN INTERLINGUA

Mesuration del Rendimento Cardiac per Medio del Contation de un Rapidemente Excernite Indicator

Le technica del externe contation precordial es un ben establite methodo pro mesurar le rendimento cardiac. Reportos in le litteratura monstra un accuratia comparabile a illo del methodo directe de Fick. Le presente communication describe un modification del technica que extende su utilitate.

Es monstrate que un rapidemente excernite indicator radio-active pote esser usate, ben que le natura de su disparition ab le sanguine non permitte un accurate mesuration del volumine de sanguine. Un modification del maniera de manipular le equation pro le calculation del rendimento cardiac resulta in un "cancellation de errores" e rende innecessari le determination del ver volumine de sanguine.

Le indicator usate in le studios hic reportate esseva Cholografin a I_{131}. Esseva trovate que illo ha, al media, un periodo de medie valor biologic in le sanguine de 5,34 horas. In comparation con albumina a I_{131}, le radiation recipite per le patiente es assi reducite a un vintesimo, e plus frequente determinationes es consequentemente possibile.

Determinationes duplicate del rendimento cardiac con le uso de Cholografin a I_{131} monstrava un deviation standard ab le valor medie de 3,91%. Isto esseva simile al deviation standard trovate in le comparation de Cholografin a I_{131} con albumina a I_{131} (3,47%) e a illo in determinationes duplicate con albumina a I_{131} (3,24%). Assi il pare que le replicabilitate del mesuration del rendimento cardiac e le magnitude del valores obtenite con Chlorografin a I_{131} es comparabile a illos mentionate pro le methodo directe de Fick in reportos in que le methodo directe de Fick es comparate con le technica del contation precordial.

ERYTHROCYTE SEDIMENTATION RATE IN VARIOUS HEMOGLOBINOPATHIES

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The finding of a low erythrocyte sedimentation rate suggests a number of disease states, most of which are associated with hypofibrinogenemia. Among the more unusual disease entities known to be associated with retarded erythrocyte sedimentation is sickle cell disease (Winsor and Burch[5], Wintrobe[6]). Recently, in studying a group of patients with homozygous C(CC) disease, it was incidentally noted that their red blood cell sedimentation was virtually nil. These observations led to an investigation of the association of a diminished erythrocyte sedimentation rate with various hemoglobinopathies.

Method. Records of hemoglobin electrophoresis at the Wadsworth Veterans Administration and University of California at Los Angeles Hospitals since 1955 were studied. The corresponding charts were reviewed and those patients for whom an erythrocyte sedimentation rate had been obtained were included in our report. The controversial question of whether or not to correct the sedimentation rate has been avoided and both corrected and uncorrected values have been included.

Results. As shown in Table 1, all of the 6 cases of homozygous C disease had a low erythrocyte sedimentation rate with 5 of the group being zero uncorrected. The sedimentation test was repeated in the first 3 cases using the Westergren method and was again found to be zero uncorrected in one hour. Three of the 8 patients with SC hemoglobin had uncorrected sedimentation rates of zero. Most of the CC and SC hemoglobin patients did not have a disease known to be associated with an elevated sedimentation rate.

None of the 6 cases of sickle cell disease had a low sedimentation rate although 3 corrected to zero. All of these patients were seriously ill.

Table 2 depicts patients with sickle cell trait and hemoglobin C trait as well as a control group of patients with normal hemoglobin patterns. The erythrocyte sedimentation rate showed no definite trend in any of these groups.

Graphic illustration of these findings is presented in Fig. 1.

Discussion. The present study indicates that a diminished erythrocyte sedimentation rate is found in hemoglobinopathies other than sickle cell disease. Five of the 6 cases of homozygous C disease studied were found to have no red cell sedimentation at the end of one hour. The other hemoglobinopathies were not so striking in this regard.

The low erythrocyte sedimentation rate in sickle cell disease has been attributed to decreased rouleaux formation resulting from the abnormal shape

TABLE 1.—ERYTHROCYTE SEDIMENTATION RATE IN HOMOZYGOUS C, S, AND SC DISEASES

Patient	*Hgb°*	*Hct*	*Uncorrected ESR (Wintrobe)*	*Corrected ESR (Wintrobe-Landsberg)*	*Remarks*
E.F.(M)	CC	38	0	0	Acute gastroenteritis. Marked anisocytosis. 20% targeting.
H.F.(M)	CC	38	0	0	Asymptomatic brother of E.F. Marked anisocytosis, 50% targeting.
J.F.(M)	CC	39	0	0	Brother of E.F. Marked anisocytosis, 40% targeting.
H.F.(M)	CC	40	2	0	Asymptomatic 81 yr. old father of 3 pts. listed above. Moderate anisocytosis, 40% targeting.
W.L.(M)	CC	42	0	0	Hematuria; marked anisocytosis, 40% targeting.
W.K.(M)	CC	34	0	0	Acute bacterial pneumonia. Marked anisocytosis, 30% targeting.
W.C.(M)	SS	30	28	5	Crisis.
		30	47	18	Bony infarct.
		24	32	0	Crisis
B.K.(F)	SS	30	32	8	Possible peptic ulcer.
O.T.(F)	SS	34	36	16	Crisis.
F.J.(M)	SS	24	35	2	Asymptomatic.
B.H.(F)	SS	17	25	0	Acute pneumonia and crisis.
F.O.(M)	SS	32	7	0	Crisis.
C.C.(M)	SC	44	4	2	Seminal vesiculitis; 40% targeting.
E B.(M)	SC	47	0	0	Chorioretinitis; marked anisocytosis; 50% targeting.
M.B.(M)	SC	40	0	0	Vitreous hemorrhage on both occasions.
		40	20	11	
A.T.(M)	SC	35	13	0	Asymptomatic; marked anisocytosis; 30% targeting.
R.J.(M)	SC	40	8	2	Asymptomatic; 50% targeting.
		41	0	0	
D.D.(M)	SC	31	42	16	Osteomyelitis.
E.H.(M)	SC	36	12	0	Abdominal pain of unknown cause; 50% targeting.
		42	6	1	
T.D.(M)	SC	34	27	5	Acute pyelonephritis.

°Paper strip hemoglobin electrophoresis.

of the cells. Bunting[3] exposed SS and SA blood to carbon dioxide and found an increase in the sickling phenomenon attended by an inhibition of rouleaux formation and a decrease in the sedimentation rate. On the other hand, oxygenated blood showed good rouleaux formation and a normal sedimentation rate.

The finding of a very low sedimentation rate in a nonsickle cell hemoglobinopathy, namely homozygous C disease, has no ready explanation. An investigation of the various mechanisms

TABLE 2.—ERYTHROCYTE SEDIMENTATION RATE IN OTHER HEMOGLOBIN COMBINATIONS

Patient	*Hgb°*	*Hct*	*Uncorrected ESR (Wintrobe)*	*Corrected ESR (Wintrobe-Landsberg)*	*Remarks*
S.D.(M)	AC	43	14	9	Congestive Heart failure.
		43	14	10	
		43	39	32	
G.F.(M)	AC	47	3	2	Asymptomatic; brother of family study listed in Table 1.
G.K.(M)	AC	43	11	7	Asymptomatic.
L.W.(M)	AC	16	84	22	Active TBC of lungs and kidneys.
A.C.(M)	AS	24–36	32–12	0	Lead poisoning.
W.B.(M)	AS	42	9	6	Asymptomatic.
L.H.(M)	AS	25	75	39	Upper G.I. bleeding.
L.G.(M)	AS	36	12	0	Hematuria.
N.B.(M)	AS	45	3	2	Duodenal ulcer.
W.L.(M)	AS	48	10	9	Acute bacterial pneumonia.
R.G.(M)	AS	37	14	3	Seminal vesiculitis.
		37	58	39	
G.H.(M)	AS	32	38	14	Hematuria.
J.T.(M)	AS	48	5	4	Cerebral vascular thrombosis.
		50	20	15	
L.L.(M)	AS	39	16	7	Duodenal ulcer.
R.S.(M)	AS	36	56	34	Cancer of lung with acute pneumonia.
R.S.(M)	AS	38	10	2	Duodenal ulcer and serum hepatitis.
		42	30	25	
R.D.(F)	AS	36	16	8	Spontaneous abortion.
E.I.(F)	AS	31	52	30	Spontaneous abortion.
R.S.(M)	AS	38	60	48	Acute bacterial pneumonia.
R.H.(M)	SD	23	35	0	Crisis; splenectomy for "anemia" in youth.
F.I.(M)	FA	42	0 (on many occasions)	0	12% fetal hemoglobin; duodenal ulcer and Strongyloidiasis; 50% targeting; moderate anisocytosis.
(Fifty-six others)	AA	38–44	7–43	3–28	Group of 11 pts. on a gen. med. ward, with disease not known to be associated with an increased ESR.

°Paper strip hemoglobin electrophoresis.

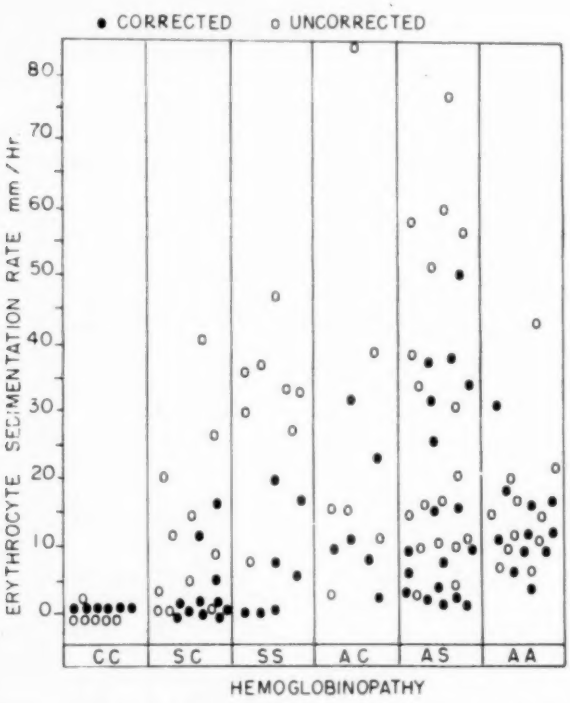

Fig. 1.—Pictorial representation of the Erythrocyte Sedimentation Rate in 41 patients with various hemoglobin electrophoretic patterns.

responsible for the decreased red cell sedimentation in the hemoglobinopathies will be the subject of a future report and only a few brief speculations on the problem will be presented here.

Targeting of the red blood cell is a prominent feature in patients with C hemoglobin. Each of the three disorders associated with the low sedimentation rate is distinguished by a particular corpuscular form under the microscope (the sickle cell in SS, the target cell in CC, and both types in SC). Furthermore, in all three disorders, there is a high degree of anisocytosis and poikilocytosis which may interfere with rouleaux formation sufficiently to explain the decreased sedimentation rate.

Poole and Summers[4], interchanged the erythrocytes and plasma of normal and anemic subjects (in various symptomatic anemias) and showed that the "anemic cells" sedimented more slowly than did the normal cells, both in normal plasma and in the plasma of anemic individuals. Both types of cells sedimented more rapidly in the plasma of anemic patients. They concluded that the anemic cells have a retarding influence and the anemic plasma an accelerating influence on the sedimentation rate. It was their opinion that anisocytosis was responsible for the cell retarding effect, but no direct evidence for this was offered. Perhaps the retarding effect due to abnormalities in the shape of the red cells in the hemoglobinopathies under discussion are not

counteracted by the plasma accelerating factors found in other anemias. A low sedimentation rate would be the result.

The study of one patient's plasma (E.F., Table 1) by electrophoresis and plasma fibrinogen determinations showed no decrease in fibrinogen, no decrease in alpha, beta or gamma globulin, and no increase in serum albumin. It was concluded that the plasma factors commonly thought of as influencing the sedimentation rate did not play a role in causing the zero erythrocyte sedimentation rate in this patient.

Haptoglobin (the hemoglobin-binding globulin) is increased in disease states associated with high sedimentation rates and decreased in hemolytic anemias (Allison and Blumberg[1], Brus and Lewis[2]). The low sedimentation rate in hemoglobinopathies may be related to decreased haptoglobin levels.

Summary. The erythrocyte sedimentation rates of 41 patients with various hemoglobin electrophoretic patterns were studied. A low erythrocyte sedimentation rate was noted in certain hemoglobinopathies. This finding was most pronounced in homozygous C disease.

Possible explanations, including the role of intracorpuscular factors (particularly abnormalities in red cell shape) and of extracorpuscular factors were discussed.

It is concluded that certain hemoglobinopathies should be included in the differential diagnosis of the low sedimentation rate.

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SUMMARIO IN INTERLINGUA

Le Sedimentation del Erythrocytos in Varie Hemoglobinopathias

Esseva studiate le sedimentation del erythrocytos in 41 patientes con varie configurationes electrophoretic pro hemoglobina. Un basse valor pro le sedimentation de erythrocytos (in mm per hora) esseva notate in certe hemoglobinopathias. Iste constatation esseva le plus marcate in morbo C homozygotic.

Es discutite plure possibile explicationes, incluse le rolo de factores intracorpuscular (particularmente anormalitates del conformation erythrocytic) e de factores extracorpuscular.

Es concludite que certe hemoglobinopathias deberea esser includite in le diagnose differential de basse valores de sedimentation erythrocytic.

THE SEASONAL INCIDENCE OF MYOCARDIAL INFARCTION IN NEW ORLEANS*

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Reports on the seasonal incidence of coronary occlusion have been published for many large cities of the United States (Table 1) (Bean[1], Bean and Mills[2], Hedley[7], Hoxie[9], Master, Dack and Jaffe[10], Mintz and Katz[11], Mullins[12], Smith, Keyes and Denham[13], Weiss[15], Wood and Hedley[16]). However, only one study of the seasonal incidence of coronary occlusion is available for a subtropical American city, Dallas (Heyer, Teng and Barris[8]). With the exception of this latter study the majority of investigators have found the incidence of coronary occlusion to be lowest during the summer and to be highest during the late fall, winter and early spring.

The New Orleans climate is characterized by mild winters and hot and humid summers. For example, during the 4 years from 1952 through 1955 only 0.2% of the days had a minimal temperature recorded of 32° F. or below, whereas 22.5% of the days had a maximal temperature of 90° F. or above. During those same years a maximal temperature of 90° F. or above was recorded for 67%, 65% and 76% of the days during June, July and August, respectively (Table 2). Because of the subtropical summers it was decided to study the incidence of myocardial infarction for New Orleans.

Materials and Methods. The clinical records of all of the patients admitted to the Charity Hospital of New Orleans with a diagnosis of acute myocardial infarction for the years 1952 through 1955 were studied. During this 4-year period the diagnosis of acute myocardial infarction was made on 1,582 occasions on the basis of the clinical data, including the patient's history, physical examination, electrocardiogram, laboratory findings and hospital course. However, although the clinical evidence strongly supported the diagnosis of myocardial infarction, electrocardiographic proof was lacking in 490 of these instances because 1) the patient expired before the electrocardiogram could be obtained (162 cases), 2) the electrocardiogram was missing from the clinical record (187 cases), or 3) the electrocardiogram failed to demonstrate evidence of myocardial infarction (141 cases). Thus, with elimination of these 490 there were 1,092 instances of myocardial infarction in which there was electrocardiographic proof of the diagnosis. Such proof consisted of a) the classical signs of myocardial infarction and b) presence of an abnormality in conduction in a patient who had had a previous electrocardiogram displaying normal conduction. However, many of the patients eliminated had classical clinical evidence of myocardial infarction. Furthermore, it is well recognized that it is possible to sustain a myocardial infarction without confirmatory electrocardiographic findings. Therefore, both groups of data were studied. The first group included

*Supported by grants from the U.S. Public Health Service.

TABLE 1.—MONTHLY DISTRIBUTION OF CASES EXPRESSED AS % OF TOTAL

	Years	*Location*	*Number of Cases*	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*Month with Greatest Incidence*
Wood and Hedley[16]	1932–34	Philadelphia	133	14.3	9.8	6.0	5.3	8.3	0.7	5.3	3.0	11.3	10.5	14.3	11.3	November
Bean and Mills[2]	1922–36	Cincinnati	278	11.2	9.2	8.4	8.2	8.4	6.1	7.0	5.7	8.4	8.1	9.3	10.0	January
Master *et al.*[10]	1930–36	New York City	612	12.3	7.0	7.9	7.9	9.1	7.2	8.9	8.1	7.5	7.5	6.3	10.3	January
Weiss[15]		Kentuckiana Area	752	8.9	8.2	9.3	9.4	7.6	8.5	7.6	8.2	7.3	7.4	6.8	10.7	December
Bean[1]	1906–36	Boston	247	8.0	7.3	10.5	11.7	8.0	5.3	4.5	4.5	11.3	7.7	10.1	10.9	April
Hoxie[9]	1929–39	Los Angeles	485	7.9	8.7	10.6	8.5	7.7	7.5	8.1	7.1	5.1	5.9	8.7	14.2	December
Mullins[12]	1928–35	Pittsburgh	369	9.5	13.6	8.4	7.6	7.3	7.9	6.5	4.9	7.0	7.9	10.0	9.5	February
Hedley[7]	1933–37	Philadelphia	5,116	9.6	9.2	9.1	9.1	7.5	6.5	6.2	5.7	6.8	9.2	9.6	11.0	December
Mintz and Katz[11]	1940–45	Chicago	572	8.2	8.0	7.3	7.3	7.5	8.2	7.2	8.0	9.6	9.0	10.7	9.3	November
Smith *et al.*[13]	1925–29	Detroit	920	8.7	7.4	9.5	7.3	8.3	7.0	8.9	8.3	9.5	7.3	10.2	7.6	November
TOTALS (Northern Cities)			9,484	9.9	8.8	8.7	8.2	8.0	6.5	7.0	6.4	8.4	8.1	9.6	10.5	December
Heyer *et al.*[8]	1946–51	Dallas	1,386	7.9	7.2	8.4	8.2	6.9	8.6	10.9	9.0	8.4	7.9	8.6	7.9	July
Present Series	1952–55	New Orleans														
All Patients Studied			1,582	8.7	8.8	8.5	8.2	7.9	7.0	8.9	10.5	8.6	7.4	8.4	6.9	August
Patients with EKG Confirmation			1,092	8.5	8.6	8.2	8.1	7.6	7.5	10.1	9.7	8.8	7.6	8.0	7.3	July
TOTALS* (Southern Cities)			2,968	8.3	8.0	8.5	8.2	7.4	7.8	9.9	9.8	8.5	7.7	8.5	7.4	July

*Totals include the series of Heyer, Teng and Barris[8] and all of the patients studied in the present series.

TABLE 2.—SUMMARY OF METEOROLOGICAL DATA FOR YEARS 1952–1955 NEW ORLEANS, LOUISIANA

	Jan.	*Feb.*	*March*	*April*	*May*	*June*	*July*	*Aug.*	*Sept.*	*Oct.*	*Nov.*	*Dec.*
Average Temperature	58.0	59.4	64.3	70.7	76.8	83.0	83.2	83.9	80.7	70.9	60.7	55.6
Average Relative Humidity	87.2	86.5	84.0	86.0	88.0	89.0	91.0	91.2	87.6	84.5	83.5	84.6
Percentage of Days with Maximum Temperature of 90° F. or above	—	—	—	1	20	67	65	76	53	8	—	—
Percentage of Days with Minimum Temperature of 32° F. or below	—	—	1	—	—	—	—	—	—	—	—	3

all patients with typical clinical evidence of myocardial infarction, whereas in the second group only patients with electrocardiographic evidence of myocardial infarction were included.

Results. The results are summarized in Tables 1 and 2 and Figs. 1 to 3.

ing September, October and December. A minor secondary peak was present in November (Fig. 1). The over-all mortality rate was 28%, with the highest rate during the month of August (37%) and a secondary peak present in February (34%).

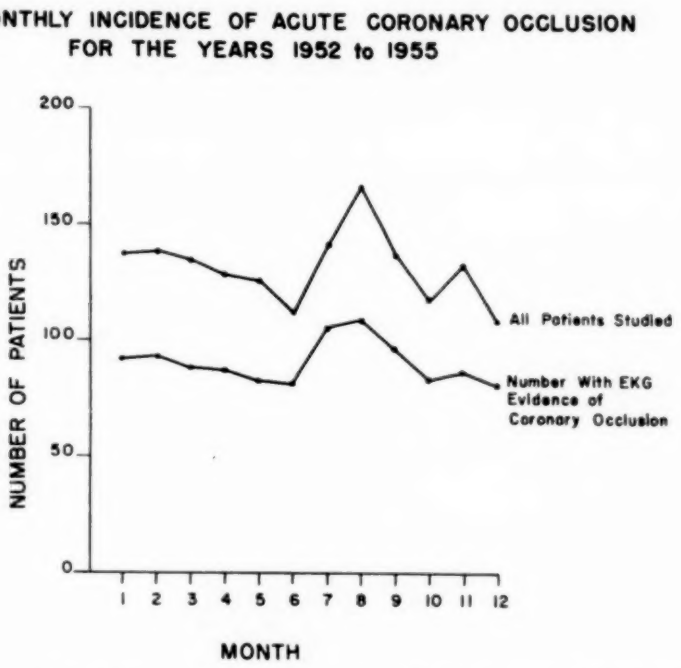

Fig. 1.—The monthly incidence of acute coronary occlusion in New Orleans for the years 1952 through 1955 for the entire series of 1,582 patients with myocardial infarction and for the 1,092 patients in whom there was reliable electrocardiographic evidence of myocardial infarction.

During the years 1952 through 1955, patients with clinical evidence of acute myocardial infarction were admitted to the Charity Hospital in New Orleans on 1,582 occasions. The greatest number of patients was admitted during August and the fewest number during December. There was a tendency for the incidence of coronary occlusion to decline gradually from January to June, to increase in July and August, and then to decline again dur-

The data for the 1,092 instances of acute coronary occlusion with diagnostic electrocardiographic evidence of myocardial infarction were essentially similar to those described for the patients with the typical clinical picture of myocardial infarction. However, the percentage of patients with positive electrocardiographic findings of myocardial infarction was slightly higher in July and August than was the percentage of patients with clinical evi-

dence of myocardial infarction (Fig. 1).

The incidence of myocardial infarction was also determined for the years 1941 through 1943 to learn the influence of the introduction of antibiotics on the seasonal incidence of myocardial infarction. The reliability of the data for the years 1941 through 1943 cannot be considered to be commensurate with that for the years 1952 through 1955 since only the standard electrocardiographic leads were usually recorded. Nevertheless, certain qualitative differences in incidence in the two series noted may be important. During the years 1941 through 1943 the greatest number of patients with myocardial infarction was admitted to hospital in February with secondary peaks in April and August.

Discussion. This study of the seasonal influence on the incidence of myocardial infarction combined with that of Heyer, Teng and Barris[8] from Dallas provides an opportunity to compare two series from southern cities with a large number of northern cities (Table 1, Figs. 1, 2). Los Angeles was included with the northern cities because the climate is cool during the evenings in the summer. In fact, during the 10-year period over which the Los Angeles study extended the mean temperature recorded for June, July and August was 70.3° F. (Hoxie[9]), whereas the mean temperature recorded in New Orleans for the same months was 83.3° F.

The seasonal incidence of coronary occlusion in New Orleans and Dallas was remarkably similar (Fig. 3) but quite different from that found in cities with temperate weather (Fig. 2).

The adverse effects of a hot and

MONTHLY INCIDENCE OF ACUTE CORONARY OCCLUSION FOR THE NORTHERN AND SOUTHERN CITIES STUDIED

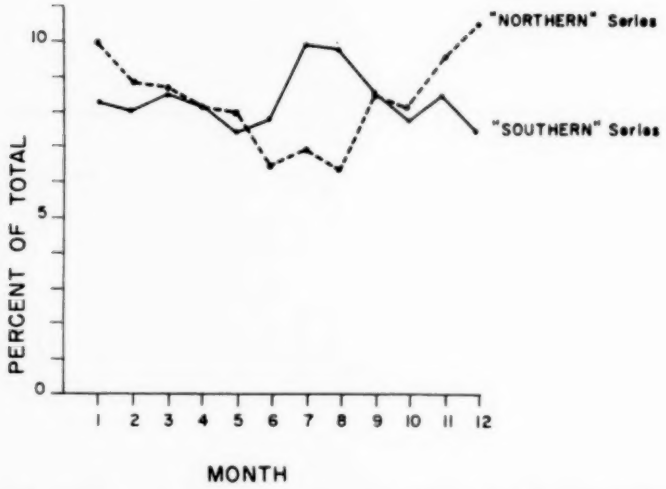

Fig. 2.—The monthly incidence of acute coronary occlusion in a "northern" and a "southern" series of patients. The cities included in each of the series are shown in Table 1.

humid environment on the cardiovascular system of man have been described in previous reports from this laboratory (Berenson and Burch[3], Burch[4], Burch *et al.*[5], Burch and Hyman[6]). A hot and humid, or an excessively cold climate, places a burden on the cardiovascular system in that cardiac output and work increase in the first instance in order to dissipate heat and in the second instance to support an increase in metabolic rate.

It is not necessary to live in the subtropical climatic zone to experience subtropical weather. Indeed, the majority of the larger cities in this country have episodes of intense subtropical weather during the summer months. During these tropical inflows (heat waves) the incidence of myocardial infarction increases (Teng and Heyer[14]). The reason the incidence of myocardial infarction is not higher in the summer in the temperate zone is probably related to the fact that "heat waves" are of relatively short duration and that during periods of seasonal summer weather the cool nights relieve the heart of the burden of heat stress.

The mortality rate in the present series was highest during the month of August. Studies performed on the wards of the Charity Hospital during the months of July and August (1957-1958) showed that cardiac output and work for the same patient were higher for a non-air-conditioned ward exposed to the summer weather than for a comfortably cool air-conditioned ward (Burch *et al.*[5]).

The data for 1941 through 1943 indicated a higher percentage incidence of myocardial infarction during the winter than the summer although there was a

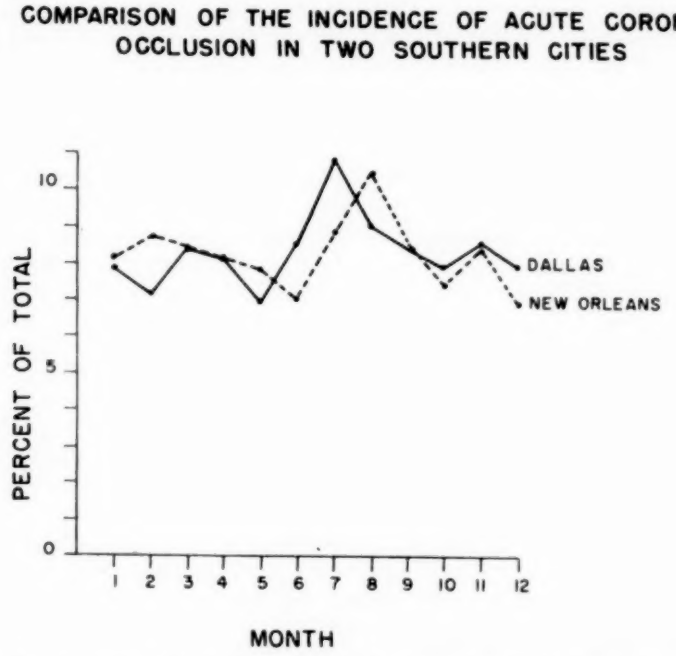

Fig. 3.—A comparison of the incidence of acute coronary occlusion for two cities with subtropical climates.

secondary peak for July and August. A possible explanation for the monthly differences in the incidence of myocardial infarction found between the years 1941 and 1943 and 1952 and 1955 may be due to the availability of effective antibiotics during the latter period. Today patients with cardiac disease survive the stress of respiratory infection better because of antibiotic agents. In the northern United States the climatic stress of the winter overshadows the stress of infection, whereas the thermal stress offered by the summer weather tends to be milder and less prolonged.

Although the weather is relatively hot and humid during the month of June in New Orleans, the incidence of coronary occlusion did not increase until July and August. It would appear that thermal stress has a "cumulative effect" with the incidence and degree of decompensation increasing as the summer wears on, reaching a peak in August.

Summary. The seasonal incidence of acute coronary occlusion in New Orleans was studied. During the years 1952 through 1955, 1,582 patients were admitted to the Charity Hospital with acute coronary occlusion. The month with the greatest incidence of coronary occlusion as well as the highest death rate was August. August was also the hottest and most humid month.

Although many factors are important in determining the incidence of coronary occlusion, the influence of the weather and climate cannot be ignored. The differences between the seasonal incidence of acute myocardial infarction for the North and South demonstrate the importance of climatic influences on the cardiovascular system.

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(Interlingua on page 480)

CARBOHYDRATE METABOLISM IN HEALTHY OLD MEN AND WOMEN OVER 70 YEARS OF AGE

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In connection with our program of studying biochemical changes occurring in healthy old men and women living at the Masonic Home and Hospital in Wallingford, Connecticut, it was decided to investigate some aspects of carbohydrate metabolism by means of certain blood chemistry determinations. By "healthy" we mean no incapacitating organic diseases tending to produce uremia, acidosis, or complicated heart diseases, but not including many conditions common to old age such as osteoporosis, general arteriosclerosis and its sequelae such as hypertension and mental disturbances.

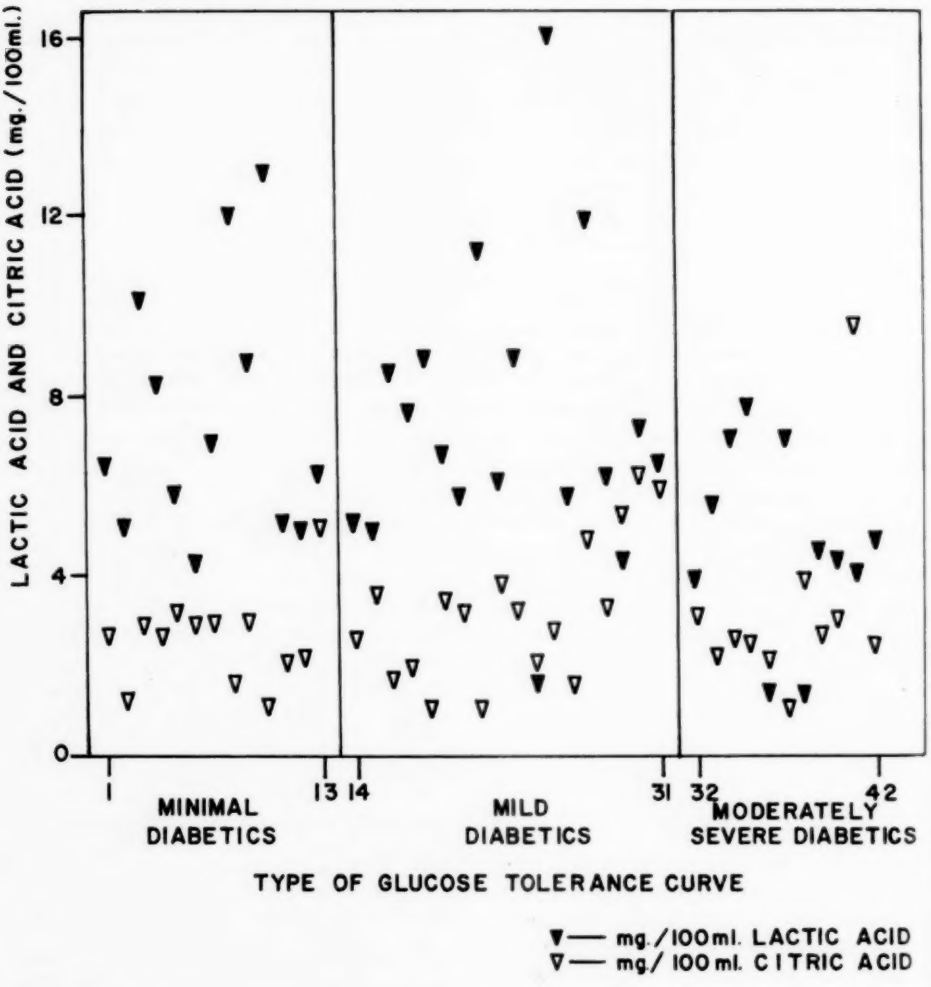
The blood chemistry tests performed were either the standard 3-hour glucose tolerance or merely a fasting blood sugar when the subject was too nervous to ingest the oral glucose solution. Also included were lactic acid, citric acid, inorganic phosphorus, adenosine triphosphate phosphorus, total organic acid soluble phosphorus, and the sum of adenylic acid, hexose phosphate, and diphosphoglyceric acid phosphorus. The glucose tolerance test is, of course, suggestive of insulin secretion as affected by adrenal and pituitary function if the absorption of glucose is considered to be normal. Lactic acid and the organic acid soluble phosphates are indicative of the oxidative phosphorylation of glucose to pyruvic acid. Citric acid is an intermediate in the Krebs tricarboxylic acid cycle which accomplished the aerobic oxidation of some of the pyruvic acid to carbon dioxide.

The diet of the old men and women was adequate, averaging 2200 calories per day. However, in many cases the fluid intake was low as indicated by a subnormal urinary output of less than 700 ml. per day. None of the subjects included in this study was a known diabetic and none received insulin therapy, although several were known to be "sugar spillers" as revealed by routine urine examinations.

Methods. Forty-nine men and women over 70 years of age were studied. On 42 of these a standard 3-hour glucose tolerance test was performed, on 7, only a fasting blood sugar determination was done for the reason previously given. In all cases, a lactic acid, citric acid, inorganic phosphorus, and organic acid soluble phosphates were also run on the fasting blood sample taken during the glucose tolerance test. The old people were not prepared in any special manner for the above tests, except that they partook adequately of the food served them for several days previous to the tests.

Since subsequent results revealed abnormalities in the glucose tolerance curves, two groups of controls were also included in this study. Each group consisted of ambulatory men and women under 50 years of age. The first group had either a normal glucose toler-

FIGURE 1. **A COMPARISON OF THE BLOOD LACTIC ACID AND CITRIC ACID LEVELS WITH THE TYPE OF DIABETIC CURVE OBTAINED IN 42 HEALTHY OLD MEN AND WOMEN OVER 70 YEARS OF AGE**



ance curve or a normal 2-hour postprandial blood sugar determination, while in the second group the glucose tolerance curve or fasting blood sugar determination was somewhat elevated; no insulin therapy being taken. The purpose of the two control groups was to compare the blood chemistry results obtained in the old folks with those obtained both in normal younger people and in younger people with a slightly disturbed carbohydrate metabolism.

The method of Folin and Wu[4] was used to perform blood sugar determinations. Blood lactic acid was determined by the method described in " Clinical Chemistry Microtechniques for Routine Laboratory" (Natelson[6]), while the method of Natelson, Lugovoy and Pincus[7] was used to obtain blood citric acid levels. Blood inorganic phosphorus was determined by the method of Fiske and Subbarrow[3] while the method of Gottfried and Eidman[5] was used to determine the blood organic acid soluble phosphate fractions.

TABLE 1.—GLUCOSE TOLERANCE CURVES AND FASTING BLOOD SUGARS ON 49 HEALTHY MEN AND WOMEN OVER 70 YEARS OF AGE

SUBJECT	AGE	TYPE OF CURVE	FASTING (mg./100ml.)	30 min. (mg./100ml.)	60 min. (mg./100ml.)	120 min. (mg./100ml.)	180 min. (mg./100ml.)
1	87	X	108	151	179	163	136
2	76	X	118	163	176	129	114
3	79	X	109	135	141	158	181
4	81	X	124	141	145	189	139
5	85	X	120	220	188	129	110
6	83	X	125	167	173	137	112
7	81	X	140	186	199	167	145
8	72	X	104	135	190	157	145
9	89	X	108	172	137	135	127
10	70	X	85	172	210	129	91
11	87	X	120	163	189	172	145
12	81	X	106	150	200	182	110
13	87	X	100	153	174	153	134
14	85	XX	134	199	238	181	84
15	82	XX	122	172	220	186	176
16	89	XX	118	153	202	172	167
17	85	XX	153	242	235	214	165
18	90	XX	105	138	163	256	245
19	82	XX	165	238	212	145	100
20	89	XX	106	188	235	214	158
21	71	XX	137	253	232	188	100
22	70	XX	111	196	220	186	114
23	76	XX	141	169	245	238	167
24	88	XX	137	222	275	209	129
25	71	XX	104	181	202	181	102
26	78	XX	132	206	212	178	176
27	91	XX	104	149	232	223	167
28	90	XX	118	147	170	209	172
29	75	XX	104	226	264	194	170
30	74	XX	109	181	199	209	130
31	88	XX	114	153	226	220	158
32	81	XXX	120	167	212	268	290
33	73	XXX	147	253	300	238	158
34	78	XXX	122	186	253	291	300
35	81	XXX	188	283	363	382	352
36	76	XXX	122	191	253	300	220
37	89	XXX	134	250	363	238	163
38	84	XXX	108	188	300	295	214
39	86	XXX	94	113	245	290	176
40	80	XXX	112	214	330	283	80
41	82	XXX	125	186	268	268	202
42	70	XXX	179	245	330	383	238
43	81		130				
44	87		134				
45	82		141				
46	93		137				
47	85		120				
48	83		90				
49	92		100				

X—Minimal Diabetic XX—Mild Diabetic XXX—Moderately Severe Diabetic

TABLE 2. BLOOD LACTIC ACID, INORGANIC PHOSPHORUS, ADENOSINE TRIPHOSPHATE PHOSPHORUS, THE SUM OF ADENYLIC ACID + HEXOSE PHOSPHATE + DIPHOSPHOGLYCERIC ACID PHOSPHORUS, TOTAL ORGANIC ACID SOLUBLE PHOSPHORUS, AND CITRIC ACID IN HEALTHY MEN AND WOMEN.

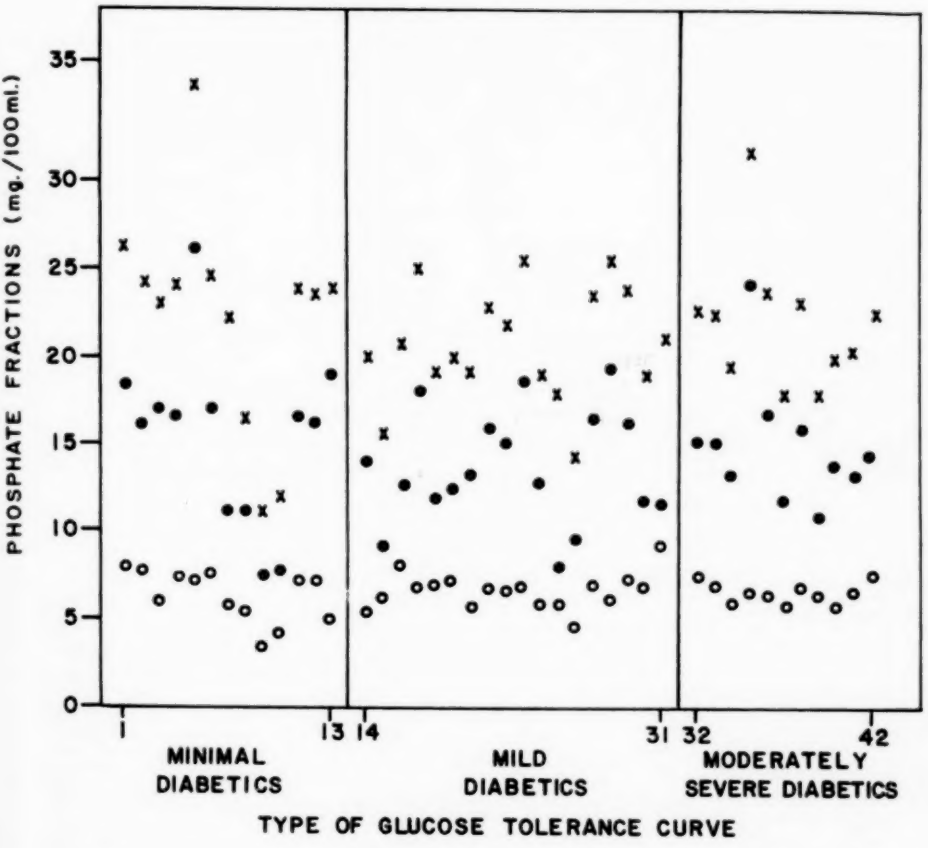
	49 HEALTHY OLD MEN AND WOMEN OVER 70 YEARS OF AGE		6 NORMAL CONTROLS UNDER 50 YEARS OF AGE HAVING EITHER A NORMAL GLUCOSE TOLERANCE CURVE OR A NORMAL 2 HOUR POST PRANDIAL SUGAR.		5 NORMAL CONTROLS UNDER 50 YEARS OF AGE HAVING EITHER A SLIGHTLY ELEVATED FASTING SUGAR, 2 HOUR POST PRANDIAL SUGAR OR GLUCOSE TOLERANCE	
DETERMINATION	RANGE mg./100ml.	MEAN mg./100ml.	RANGE mg./100ml.	MEAN mg./100ml.	RANGE mg./100ml.	MEAN mg./100ml.
LACTIC ACID	1.4–16.1	7.2±2.6	1.9–10.6	6.9±3.0	2.7–8.9	5.4±1.5
INORGANIC PHOSPHORUS	2.3–5.8	3.2±0.5	3.2–4.0	3.6±0.3	3.2–4.0	3.7±0.3
ADENOSINE TRIPHOSPHATE PHOSPHORUS	3.5–9.6	6.8±0.8	5.8–8.0	6.6±0.7	5.4–8.8	6.1±1.3
ADENYLIC ACID P + HEXOSE PHOSPHATE P + DI PHOSPHOGLYCERIC ACID P	8.1–26.3	15.2±3.0	13.2–22.6	17.2±3.1	13.5–21.9	17.2±2.8
TOTAL ORGANIC ACID SOLUBLE PHOSPHORUS	11.0–33.6	22.1±3.2	19.0–28.8	23.8±3.0	18.9–28.8	24.1±2.8
CITRIC ACID	1.1–9.6	3.0±1.0	1.1–1.3	2.2±0.9	0.9–7.5	3.2±1.8

Results and Discussions. The glucose tolerance curve and the fasting blood sugar determinations are listed in Table 1. Every one of the glucose tolerance curves was abnormal, ranging from a slightly diabetic curve to a moderately diabetic curve indicating a need for insulin therapy. The 42 glucose tolerance curves in Table 1 are arbitrarily divided into three groups, minimal, mild and moderately severe diabetic. Of the 7 remaining cases in which no complete tolerance test was performed, 4 of the fasting blood sugar determinations were somewhat elevated and 3 were normal.

The results in this study show a much higher incidence of a decreased carbohydrate tolerance in older people than that revealed by other investigators. Chesrow and Bleyer[2] obtained a positive screening test on 248 of 1000 patients over 60 years of age. When these 248 patients were given an oral glucose tolerance test similar to the one given here, only 88 abnormal curves were obtained. Brandt[1] observed that 18 of 59 elderly patients either had an elevated 2-hour postprandial blood sugar determination over 150 mg. per 100 ml. or a standard glucose tolerance curve indicative of diabetes mellitus.

In Figs. 1 and 2 an attempt has been made to correlate the various blood chemistry results obtained on the fasting blood sample of the glucose tol-

FIGURE 2. **A COMPARISON OF THE BLOOD ORGANIC ACID SOLUBLE PHOSPHATE FRACTIONS WITH THE TYPE OF DIABETIC CURVE OBTAINED IN 42 HEALTHY OLD MEN AND WOMEN OVER 70 YEARS OF AGE**



ance test with the type of diabetic curve. No apparent relation can be observed between the organic acid soluble phosphates or the citric acid and the character of the glucose tolerance curve. In the case of the lactic acid, a relation does appear to exist. Here, the lactic acid levels seem to be somewhat lower in the moderately diabetic curves than in the minimal and mild diabetic ones. However, when all the fasting blood chemistry results obtained in the old men and women are summarized and compared with those obtained in the two control series (Table 2), it becomes evident that no true relation exists between the blood lactic acid and the type of glucose tolerance curve.

Table 2 indicates that the blood lactic acid, citric acid, and organic acid soluble phosphates tend to be the same for either older or younger, normal or mildly diabetic men and women. The abnormal glucose curves which have been obtained are, therefore, the only indication of a disturbance in carbohydrate metabolism. If age does produce an impairment in the anaerobic breakdown of glucose to lactice acid or in the aerobic oxidation of pyruvic acid to carbon dioxide by means of the Krebs cycle, then the analytical methods employed in this study are not sensitive enough to detect this.

Summary. 1. Blood chemistry studies tending to reveal the existence of an impairment in carbohydrate metabolism were performed on 49 "healthy" old men and women over 70 years of age. These tests included a standard oral glucose tolerance test and fasting blood lactic acid, citric acid, and organic acid soluble phosphate fractions.

2. Forty-two of the glucose tolerance tests were completed. All were abnormal ranging from a minimal diabetic curve to a moderately diabetic curve.

3. No significant differences could be detected between the blood lactic acid, citric, and the organic acid soluble phosphate fractions in the old men and women and in two control groups of younger people, one group having a normal glucose tolerance curve, the other group having a slightly elevated glucose tolerance curve.

4. Attempts to correlate the blood lactic acid, citric acid, and the organic acid soluble phosphate fractions in the old men and women with the type of diabetic curve obtained were nonconclusive.

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SUMMARIO IN INTERLINGUA

(See page 468 for original article)

Le Incidentia Saisonal de Infarcimento Myocardial in Nove Orleans

Le incidentia saisonal de acute occlusion coronari in Nove Orleans esseva studiate. Durante le annos ab 1952 ad 1955, 1.582 patientes esseva admittite al Hospital Caritate con acute occlusion coronari. Le mense con le plus alte incidentia de occlusion coronari e etiam con le plus alter mortalitate esseva le mense de augusto. Le augusto esseva le mense le plus calide e le plus humide.

Ben que multe factores es importante in determinar le incidentia de occlusion coronari, le influentia del tempestate e climate non pote esser ignorate. Le differentias inter le incidentias saisonal de acute infarcimento myocardial in le nord e le sud del pais demonstra le signification del influentias climatic super le systema cardiovascular.

SEX AND DIABETES MELLITUS: A COMPARATIVE STUDY OF 26 NEGRO MALES AND 26 NEGRO FEMALES MATCHED FOR AGE

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In view of the preponderance of female to male diabetic patients in the outpatient department where this study was conducted, an interest was developed in making a small comparative study of a sample of these patients to see if they differed significantly from each other in terms of duration of diabetes; degree of obesity; method of control; degree of control; cardiac diagnosis; and in the use of the clinic and hospital facilities.

Very little information from studies of a controlled or an experimental nature bearing on this problem was located in the literature. However, the sex incidence of diabetes has received considerable attention and a brief review of this literature is cited.

Diabetes is the only major cause of death where female mortality (adjusted for age) is higher than the male. This differential has actually widened considerably since 1900, in the older age groups. The prevalence in women is relatively greatest at ages above 45 (Health Information Foundation[5]). There is little difference in the sex incidence in childhood, and Duncan[2] explains the higher incidence of diabetes in females on the basis that women live longer and are less active physically than men and are more prone to become obese between 40 and 70 years of age than are the men. He further states that the incidence of diabetes is higher in married than in single women over 45 years of age and especially higher in women who have borne children. Married women, according to Duncan[2], who have had children weigh more than single women and this increased body weight undoubtedly influences the incidence of diabetes unfavorably. The security enjoyed by the average married woman over 45 years of age is further proposed to influence the likelihood of gaining in body weight and hence contributes to a greater likelihood of developing diabetes. He notes that the increasing incidence of diabetes in women over 45 years of age is out of all proportion to that observed in the male population and that the increase in the mortality rate of this group over male diabetics of the same age is striking.

Williams[7] states that the sex difference in incidence of the disease is most striking in the United States and may reflect, in part, the improved economic and social level of women in this country. He also believes that the increased incidence among married women appears to parallel closely the increased incidence of obesity in this group as compared with single women.

Joslin *et al.*[4] attribute the increased diabetic incidence in women to two causes: first, the growing respect in which women are held throughout the world and the resulting greater investi-

gation and report upon their health, and second, the greater numbers that live into the age zone when diabetes is most apt to have its onset. They add that sex plays no essential factor in onset until the age of 50 years is reached or above the age of 70 years. They also state that the distinguishing feature between the sexes for ages from 40 to 60 years is the menopause. This relationship is not clarified.

Vinke *et al.*[6] reported that their findings among women indicate that obesity is a stimulating factor in the pathogenesis of diabetes mellitus and that the high frequency of diabetes among women over 50 is associated with obesity. He also reported that the unfavorable influence of obesity on diabetes is indicated by the higher insulin requirement among overweight women, who showed insufficient loss of weight during the treatment.

Clinical Material. The investigations are based on the data available from patients visiting the Diabetes Clinic of Hubbard Hospital. Twenty-six unselected male diabetic patients were matched with 26 female patients in terms of age. The data were collected during a period from September, 1959, to March, 1960, on Negro patients that had been observed in this clinic from 6 months to 10 years and were selected from a larger group of patients who were previously being studied for the incidences of arteriosclerotic heart disease (Vinke *et al.*[6]).

The patients' records were reviewed and the following data were obtained and recorded:

1. Age
2. Sex
3. Duration of Diabetes
4. Degree of Obesity
5. Method of Control
6. Degree of Control
7. Cardiac Diagnosis
8. Presence of selected cardiac conditions: angina pectoris, aortic sclerosis, cardiomegaly, myocardial infarction, congestive heart failure, and hypertensive heart disease
9. Use of outpatient and other hospital facilities

The degree of obesity was calculated, utilizing the Metropolitan Life Insurance Company tables. The reference for all patients was the average weight for a medium frame.

The patients were divided into four categories: excellent, good, fair, and poor, based on the degree of control of the diabetes. This evaluation was determined by a review of the patient's entire record. Fasting blood sugar determinations secured at various intervals, as well as urine sugar and acetone recorded on each clinic visit were available. Excellent control was recorded for those patients who exhibited no glycosuria and had a fasting blood sugar which averaged 140 mg. per 100 ml. (Folin-Wu method) or less. Good control was recorded for those patients who usually had negative urine sugars but sometimes an occasional glycosuria of not more than 0.5% and fasting blood sugars that averaged above 140 mg. per 100 ml. Fair control indicated frequent or persistent glycosuria but no acetonuria. In the group with poor control were those who, in addition to frequent or persistent glycosuria and corresponding hyperglycemia, also had infrequent ketonuria. Many of these patients had repeated bouts of diabetic acidosis.

TABLE 1.—AGE DISTRIBUTION, BY SEX

	Sex			
	Male		*Female*	
Age (Years)	*No.*	*%*	*No.*	*%*
75–79	1	3.8	2	7.7
70–74	4	15.4	3	11.5
65–69	3	11.5	3	11.5
60–64	5	19.2	5	19.2
55–59	5	19.2	5	19.2
50–54	2	7.7	2	7.7
45–49	1	3.8	1	3.8
40–44	2	7.7	2	7.7
35–39	2	7.7	2	7.7
30–34	0	—	0	—
25–29	1	3.8	1	3.8
Mean	57.6		57.8	
σ	12.4		12.7	
Mdn.	60.0		60.0	

The age distribution of the sample is shown in Table 1 by sex. The mean age and standard deviation for the males and females are 57.6 years and 12.4 years, and 57.8 years and 12.7 years respectively. Nearly one-half of these patients were in the 45 to 64-year-old group.

Results and Discussion. DURATION OF DIABETES. No significant difference was found for the mean duration of diabetes for the males and females (Table 2). The mean duration for the males was 7.0 years and for the females 8.0, with the standard deviation being 5.8 years and 5.0 years respectively. Only 11.5% of both groups had had the disease more than 16 years.

TABLE 2.—DURATION OF DIABETES, BY SEX

Duration of Diabetes (Years)	*Sex*			
	Male		*Female*	
	No.	%	*No.*	%
22–23.9	1	3.8	0	—
20–21.9	0	—	0	—
18–19.9	0	—	1	3.8
16–17.9	2	7.7	2	7.7
14–15.9	1	3.8	1	3.8
12–13.9	0	—	1	3.8
10–11.9	4	15.4	2	7.7
8– 9.9	2	7.7	2	7.7
6– 7.9	0	—	6	23.1
4– 5.9	4	15.4	4	15.4
2– 3.9	8	30.8	3	11.5
Less than 2	4	15.4	4	15.4
Mean	7.0			8.0
σ	5.8			5.0
Mdn.	9.0			6.7

OBESITY. The females were significantly more frequently obese ($p<.01$ using matched pairs technique) than the males as shown in Table 3. Fifty-two per cent of the males were not obese as compared with only 16% of the females. This finding is in agreement with those of Duncan[2], Williams[7], Joslin *et al.*[4], and Vinke *et al.*[6]. However, one may raise the question of a different reason for the obesity in a medically indigent group. More than 80% of both groups were over the age of 45. More than 73% of the women were parous and of these, more than 80% were obese, but so were 80% of the nulliparous also obese. It is very doubtful that these medically indigent patients of a minority group enjoy much security in this society. It would appear more likely that eating is one of the few pleasures available to them and further that their diets are composed of the cheaper fat and carbohydrate foods. It is further proposed that this is an inactive and nonproductive group and that inactivity and nonproductivity are conducive to a lack of emotional satisfaction and a lack of zest for living which results in further inactivity, overeating, and finally obesity. Experimentation is needed with prescribed activity and motivational programs for this group of female patients.

The male patient from this same population is much more likely to engage in regular physical labor. He is productive and may receive some satisfaction in the performance of this work, as contrasted to the female whose standards of housekeeping are low and require little expenditure of energy and, in addition it is no longer necessary

TABLE 3.—DEGREE OF OBESITY, BY SEX

Degree of Obesity (%)	*Sex*			
	Male		*Female*	
	No.	%	*No.*	%
90 and over	1*	4.0	1**	4.0
80–89			2	8.0
70–79	1	4.0	1	4.0
60–69			1	4.0
50–59			2	8.0
40–49			1	4.0
30–39	2	8.0	3	12.0
20–29	1	4.0	6	24.0
10–19	3	12.0	2	8.0
1–9	3	12.0	2	8.0
Degree unknown	1	4.0	—	
None	13	52.0	4	16.0
Total	25	100.0	25	100.0
Median		18.3		31.7

*224.5%

**134.0%

for her to perform the child-rearing functions. It is noted with interest that the most extremely obese male is unemployed.

TABLE 4.—METHOD OF CONTROL OF DIABETES, BY SEX

Method of Control	*Sex*			
	Male		*Female*	
	No.	*%*	*No.*	*%*
Tolbutamide	7	28.0	5	20.0
Insulin	17	68.0	14	56.0
Diet	1	4.0	6	24.0
Total	25	100.0	25	100.0

THERAPY. The patients in the study were being treated by diabetic diets, with or without the addition of insulin or tolbutamide. No significant difference was found for the method of control using chi square. Fifty-two per cent of all patients were being treated with insulin (Table 4).

The economic status and eating patterns make control by diet for the obese patients extremely difficult. This probably accounts for the lack of a significant difference between methods of control for these groups.

DEGREE OF CONTROL. The difference in degree of control for 20 pairs of patients controlled for age was tested using chi square. The other subjects and their controls could not be included in this evaluation because of inadequate follow-up. The difference was significant at the 2% level, with the males having better control than the females (Table 5). Twenty-five per cent of the males and none of the females were in the poor control group.

Since the female group is significantly more obese than the male group, it is expected that the female group would contain more mild diabetic patients and that these patients would be easier to control and therefore better controlled than the male group. Twenty-five per cent of the males are in the "poor control" group and this probably indicates that there are more severe diabetic patients in the male than in the female group. The explanation probably leads again to the socioeconomic and emotional status and the lowered activity level of these female patients: factors which make it difficult to obtain a therapeutic reducing diet and to deny oneself of eating, one of the few pleasures available.

CARDIAC DIAGNOSIS AND CARDIOVASCULAR FINDINGS. The males did not differ significantly from the females in terms of cardiac diagnosis. However, it can be noted from Table 6 that only 12% of the males and 16% of the females were considered to have no heart disease. Seventy-six per cent of both the males and females had either definite, probable or potential arteriosclerotic

TABLE 5.—DEGREE OF CONTROL OF DIABETES, BY SEX

Degree of Control	*Sex*			
	Male		*Female*	
	No.	*%*	*No.*	*%*
Excellent	6	30.0	4	20.0
Good	4	20.0	2	10.0
Fair	5	25.0	14	70.0
Poor	5	25.0	0	—
Total	20	100.0	20	100.0

TABLE 6.—CARDIAC DIAGNOSIS, BY SEX

Cardiac Diagnosis	*Sex*			
	Male		*Female*	
	No.	*%*	*No.*	*%*
Definite ASHD	6	24 0	7	28.0
Probable ASHD	8	32.0	7	28.0
Potential ASHD	5	20.0	5	20.0
Other	3	12.0	2	8.0
No Heart Disease	3	12.0	4	16.0
Total	25	100.0	25	100.0

TABLE 7.—PRESENCE OF OTHER CONDITIONS, BY SEX, IN PERCENTAGES

Presence	*Angina*		*Aortic Sclerosis*		*Cardiomegaly*		*Myocardial Infarction*		*Congestive Heart Disease*		*Hypertensive Heart Disease*	
	Male	*Female*	*Male*	*Female*	*Male*	*Female*	*Male*	*Female*	*Male*	*Female*	*Male*	*Female*
Yes	16.0	24.0	81.8	77.3	58.3	66.7	—	8.0	17.4	21.7	43.5	39.1
No	84.0	76.0	18.2	22.7	41.7	33.3	100.0	92.0	82.6	78.3	56.5	60.9
Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
N	25	25	22	22	24	24	25	25	23	23	23	23

(2)

heart disease. There were no significant differences between the groups for the cardiovascular findings of angina, aortic sclerosis, cardiomegaly, myocardial infarction, congestive heart failure and hypertensive heart disease. It can be noted from Table 7, that more women had angina pectoris, cardiomegaly, myocardial infarction (2 women and no men) and congestive heart failure than did the men. There was more aortic sclerosis and hypertensive heart disease in the males than in the females.

These data reconfirm the higher incidence of coronary artery disease in the female diabetic patient compared to the nondiabetic female.

There was no significant difference in the use of the hospital facilities for the two groups, with the exception that the Eye, Ear, Nose and Throat Clinic was used more often by the women ($p<.02$). A higher percentage of the females used the medical clinic, emergency service and the hospital than did the males, but this difference is not statistically significant. The use of the clinics was studied because of its possible relationship to the control of the diabetes in the subgroups.

The more frequent use of the Eye, Ear, Nose and Throat Clinic is noted in relationship to Givner's[3] finding that in equal numbers of male and female diabetics studied, twice as many females had diabetic retinopathy as males. The specific reason for attending this clinic was not studied in this sample.

Conclusion. These findings are in agreement with those of Duncan[2], Williams[7], and Vinke *et al.*[6] who state that the higher incidence of diabetes in women over the age of 50 is associated with obesity and that obesity is an important factor in improving the control of the diabetic patient. This present analysis does not allow for conclusions as to the cause of these findings but possibilities are discussed.

Summary. Twenty-six unselected male diabetic patients were matched individually with 26 female diabetic patients in terms of age. A comparative study of this sample was done to see if the sex groups differed significantly from each other in terms of duration of diabetes; degree of obesity; method of control; cardiac diagnosis; and in the use of the clinic and hospital facilities. Significant differences between the groups were found only in obesity, with the females being significantly more obese than the males, and in degree of control, with the males having significantly better control than the females.

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(Interlingua on page 453)

PROGRESS
OF
MEDICAL SCIENCE

OTO-RHINO-LARYNGOLOGY

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AIR POLLUTION AND RESPIRATORY DISEASES

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AIR pollution has long been recognized as a menace to health and comfort. The rate at which air pollution has been increasing in urban and industrial communities establishes it as one of mankind's most urgent enviromental problems. According to Drinker[6], increased population and urban crowding always generate increased air pollution. The latest census forecasts the population of the United States to be 214 million by 1970. If present population trends continue, most of the increase will occur in urban areas. If this is correct, it can only mean that large cities on both the Atlantic and Pacific seaboards, along the south shore of the Great Lakes and presumably along the large rivers, will expand until there is something close to a continuous line of municipalities from Baltimore to Portland, Maine, from San Francisco to San Diego, and from Chicago to Buffalo.

The effect of air pollution on human health, Barach[4] states, ranges from discomfort, depression and irritation of the nose, throat and eyes to loss of workdays, bronchospasm, chronic illness and death. To this list can be added pneumonia. Deaths from pneumonia in New York State, for example, have risen significantly in the past decade, with the highest mortality in New York City, where air pollution is highest. The lowest pneumonia mortality rise occurred in nonmetropolitan areas where air pollution is lightest. Indeed, areas with the heaviest air pollution load tend to rank high in death rates for a number of diseases[11]. Already available, and as yet little known to the general public, is considerable evidence linking air pollution to the increased incidence of chronic bronchitis, emphysema and lung cancer in urban and industrial areas. Air pollution asthma among American military

personnel in the Tokyo-Yokohama area in Japan has recently been described[18]. The most prominent symptoms were nocturnal cough, wheezing, and shortness of breath. The most characteristic feature was the pronounced subsidence of symptoms when patients left the endemic area.

It is axiomatic that human beings pollute their own environment. In this connection, the chief source of man-made air pollution is the burning of all kinds of fuel, a phenomenon first recorded in England more than 600 years ago following the newfound use of coal in London. Paulus[17] points out that one of the major sources results from the combustion of fuel for the production of heat, electric power and for certain industrial operations. The combustion of coal, natural gas and fuel oil provides many by-products, including dust, fly-ash, sulfur dioxide, and fluorine compounds. However, when the combustion process is incomplete, soot, smoke and carbon monoxide, among other elements, are discharged into the air. Incomplete combustion of gasoline and other types of motor fuel used in the operation of automobiles, buses and trucks accounts for many kinds of organic contaminants. Finally, various industrial processes have an inexhaustible capacity for discharging such formidable air pollutants as steel-mill dust, carbon monoxide, hydrogen sulfide and oxides of nitrogen, to enumerate an important few.

From this, declares Andelman[3], it should not be deduced that industry and transportation are the sole offenders in the production of air pollution hazards. Many residential communities are guilty of blithely compounding the menace of aerial sewage through widespread indifference, apathy and ignorance. Residential communities that lack adequate collection-and-disposal facilities for the destruction of refuse, rubbish, leaves and garbage encourage their citizens to use incinerators in the home and in the backyard. Unfortunately, some incinerators are poorly designed and operate so inefficiently as to produce vast quantities of smoke, dust, gases and odors. The widespread suburban and urban practice of burning leaves in the fall and spring adds still further to the air pollution load. Communities unable to furnish a suitable municipal incinerator or a sanitary land-fill will often inadvertently favor the use of a burning dump to further contaminate the air we breathe. In addition, there is the growing worldwide realization that nuclear atomic blasts are a source of aerial contamination. Generally, radioactive contamination of the atmosphere is currently not a large part of the problem of pollution. Nevertheless, the atmospheric load from past testing is still very large and constitutes a serious health hazard as it reaches the ground and enters the food chain. This augments in a limited way the irradiation from natural sources to which the human race has always been subjected.

Sulfur dioxide has been identified as the principal culprit in the air pollutant family; it is given off as a by-product of the combustion of industrial and domestic fuels, petroleum refining, and the incineration of garbage. Held in the soft, spongy particles of soot, it is readily oxidized into dilute sulfurous and sulfuric acid. In Greater New York, an average of 67.7 tons of soot per square mile fell each month in 1957, although the concentration in Manhattan proper averaged 102 tons per square mile per month[16]. Sulfuric acid is invisible, has a characteristic sharp odor, and irritates the nose and throat at levels of approximately 15 parts per million, although it is detectable by most persons at about 1½ parts per million. The greatest damage inflicted

by sulfuric compounds is directed at the bronchi, with ensuing erosion of the lining epithelium, submucosal edema, and thrombosis of the smaller arteries and veins. Manufacturing plant employees, who are exposed to high levels of sulfur dioxide, exhibit a high incidence of chronic respiratory disorders, dyspnea, emphysema, and fatigability. Dohan and Taylor[5] declare that a high correlation occurs between the average concentration of an air pollutant (sulfates) and the incidence of respiratory diseases in women working in five cities.

Irritation of the eyes, nose and throat as well as alterations in presumably normal human subjects can be produced experimentally by irritants ordinarily considered safe. In 1953, Amdur, Melvin and Drinker[1] demonstrated that inhalation of sulfur dioxide in low concentrations (1 to 8 ppm.), below the sensory threshold, that is, below the level at which they could be detected by smell or actual sense of irritation, produced consistent changes in respiration and pulse rate. Breathing became shallower and more rapid, the pulse rate increased, and the tidal volume decreased in normal subjects. Nelson[15], in commenting on these experiments, stated: "These results are among the first to show that levels of these pollutants approaching those found as general air contaminants can in fact produce demonstrable functional changes in man. Since the subjects did not know that they were receiving contaminated air, these effects must necessarily be involuntary physiological responses." Sim and Pattle[21] also exposed normal subjects to sulfur dioxide, sulfuric acid mist and various aldehydes, and recorded evidence of increased airway resistance and the production of rales with rhinorrhea and lacrimation. Amdur[2] discussed the synergistic action of sulfur dioxide gas and of sulfuric acid mist, showing that acid mist particles of 0.8 micron mixed with sulfur dioxide resulted in a toxic mixture that was more potent than suspensions of the acid mist alone or of the sulfur dioxide gas alone.

Along with sulfur dioxide, a chief gaseous offender in the air of large municipalities, is the ozone which results from the photochemical oxidation of hydrocarbons derived from the partial combustion of gasoline and diesel fuel[10]. While no single, easily identified agent emerges as the cause of the noxious gases, it is believed that automobile exhaust fumes are the largest single source of hydrocarbon emissions. Hydrocarbons present in exhaust fumes emanating from motor vehicles produce ozone and other oxidation products when they are acted on by sunlight in the presence of nitrogen oxides which are also released during combustion. Atmospheric concentrations above 0.2 part per million irritate the air passages, causing pain in the chest, cough, dyspnea and nausea. According to Thienes[22], levels of more than 0.1 ppm. for more than 4 hours are probably hazardous. In addition, perhaps one of the more ubiquitous pollutants is lead, with a prime source of air-borne lead in the average community derived from leaded fuels utilized in vehicular engines. Projections of future traffic volume indicate that the level of lead in community air will increase until changes in prevailing fuel or traffic conditions are affected.

The 3,4-benzypyrene and other polycyclic hydrocarbons believed to be carcinogenic are found in soot and fly-ash, and are also derived from the photochemical oxidation of hydrocarbons in motor vehicle exhausts. Measurements of the benzypyrene content of the air in 103 cities and 28 rural areas has shown that concentrations average 16 times greater in the city

than in the country. According to Falk, Miller and Kotin[7], the biological activity of soot entering the respiratory tract favors the development of cancer of the lung. In a study of the effect of cellular and plasma proteins on the evolution of benzypyrene from soot, they concluded that the plasma protein in the lungs dissolves 3,4-benzypyrene out of particles of soot, leaving the carcinogen free to be acted upon by lung tissue to form cancer.

Kotin and Falk[12] have demonstrated that irritants, although noncarcinogenic, may play a role in the development of cancer by interfering with the normal flow of mucus on the linings of the lung. In essence, the residence time of the carcinogenic material in the respiratory tract is increased by irritants which cause stoppage of mucous flow, and the carcinogen is then extracted from the site of its absorption. Hence, a substance may be taken from the respiratory tract and expired unabsorbed without carcinogenic effect. When it is added to a dust particle or in the presence of an irritating gas, it is not only absorbed but can become carcinogenic. Kotin produced cancer in experimental animals by exposing them to certain suspected hydrocarbons found in exhaust fumes and in synthetically produced smog. Auto exhaust fumes contain about 200 different hydrocarbons. He asserts, further, that atmospheric pollution "in and by itself, uniquely supplies the links necessary for the experimental induction of lung cancer. In the absence of evidence of data to the contrary, this observation coupled with the epidemiological characteristics of the disease strongly suggest a similar action for man"[19].

While Kotin's findings suggest a relationship, it should be pointed out that his experiments on laboratory animals do not conclusively prove that the suspected carcinogens cause cancer in man. Nevertheless, his experimental evidence is both as good and as controversial as other types of laboratory work on animals. Faced with a growing statewide smog problem, California has recently adopted standards for exhaust-system smog purifiers. Approved devices, it is anticipated, will substantially decrease the amount of carbon monoxide present in the exhaust stream by at least 60%, and the amount of hydrocarbons by as much as 80%.

Air pollutants may attack man in several possible ways, notably by their irritant action on mucous membranes, by specific toxic reactions which may or may not be cumulative, by allergenic activity, and by carcinogenic activity. The most significant way in which air pollution influences human health is that it irritates and damages the membranous surfaces of the body. The respiratory tract and the eyes, by virtue of their exposure to the surrounding air, are especially vulnerable. Investigations of the causes and nature of eye irritation produced by smog in California have progressed slowly. However, it is generally held today that while the eyes of susceptible persons become irritated when certain air pollutants attain high levels, objective ocular changes are not permanent.

Various English investigations emphasize that the diseases most intimately connected with air pollution are chronic bronchitis and emphysema. The death rate from chronic bronchitis in Great Britain is 34 times higher than in the United States. Thus, chronic bronchitis with its associated emphysema as a clinical entity and a cause of death has been of considerable concern to English investigators because of its exceptionally high mortality rate. Interest in bronchitis in the United States has been evoked as a result of the English experience, even though diagnostic criteria have differed in the

two countries[8]. Increased aggravation of respiratory symptoms among people afflicted by chronic bronchitis occurs during periods when smoke and sulfur dioxide impregnate the atmosphere. All this suggests that polluted air increases the life hazards of individuals already handicapped by pre-existing respiratory and cardiovascular diseases.

During the past decade many articles have described the effects of prolonged fogs and the dangerous pollution they can generate. The classic examples occurred in the Meuse Valley in Belgium, in Donora, Pennsylvania, and in London, England. Drinker asserts that these disasters were alike in that ill effects increased as the fogs persisted and by the end of their 4-day visitations the situations were truly alarming. In each instance the causes abated and then disappeared as the fogs were blown away. In general, prolonged fogs lasting for more than a single day are not unusual occurrences in Belgium, Donora or London. They arise from a combination of meteorological factors that lead to temperature inversions. In the Meuse Valley in Belgium, in 1930, a fatal smog episode accounted for the death of 60 persons and an estimated 4,000 made ill. Affected were persons of all ages and both sexes who complained of epiphora, throat irritation, hoarseness, cough, shortness of breath, a sense of constriction of the chest, nausea and some vomiting. Most persons who became ill were elderly or subject to existing cardiopulmonary conditions. In the Donora episode, 20 inhabitants died and 42.7% of the population of some 13,500 people experienced acute illness[20]. Among the 20 dead were 15 men and 5 women, a sex ratio of 3 to 1, the men paying a much heavier price than the women for inhaling noxious air. A follow-up study of the Donora population revealed that people who became ill during the disastrous 1948 episode generally had poorer health and a higher mortality rate during the following decade than did those inhabitants who were unaffected.

A month after the Donora disaster, London was blanketed by a smog of record density, an event that caused 3,500 excess respiratory and cardiac deaths among older persons, many of whom had chronic bronchitis, during a 2-week period following the record smog. London's worst fog disaster came in early December, 1952. A large number of inhabitants of Greater London became ill with respiratory symptoms and evinced signs of dyspnea, cyanosis and bronchospasm[9]. Retrospective analysis of death registries disclosed an excess of 4,000 deaths for the 2-week period bracketing this episode. A more recent episode occurred in London during the winter of 1957, accounting for an increase in over the customary mortality rate by 760 to 1,000. In the United States, air pollution episodes in recent years have affected persons with known asthma in New Orleans and Los Angeles. It is quite likely that other air pollution episodes have gone by unrecorded in various parts of the United States, especially where large-scale death did not result and where other factors present were assigned the blame.

Several factors enter into fog and smog formation descending over urban and industrial areas. In the United States, dense fogs often blanket large sections as moist ocean or Gulf air meet a slowly moving cold front. Fogs occur more frequently along sea coasts, but will occasionally hide large sections of the continent's interior from view. In addition, there are nocturnal fogs which invade lowlands and valleys, affecting industrial and business sections located in their midst. Late nocturnal and early morning smog formations are common, subjecting their inhabitants to frequent episodes

of stagnant, polluted air. The weather strongly influences community air pollution and is felt in terms of high and low pressure areas, precipitation, wind, turbulence, and temperature variations. Local topography modifies wind speed and direction and influences temperature. In attempting to modify or control air pollution, locale and topographic factors are important considerations.

In a discussion of procedures that would make cities more habitable, Linsky[13] states: "We cannot change the hills, valleys, bays, slow winds, wind-fogs, sunny days, and other geographical or climatic features that prevail in areas where man has built his cities. We can make those cities habitable and enjoyable, however, by persuading people to clean up their present source of air pollution and to take further preventive measures to avoid additional pollution." In this connection, a major attack on air pollution rests on the development of chemical and engineering methods to combat the adverse effects of the combustion process and to reduce the particulants in stack gases, motor exhaust gases, and in fly-ash. Fortunately, many industrial concerns today are voluntarily installing devices for the cleansing of various types of gases.

Of necessity, air pollution must be controlled at the source, and this falls into three categories: public, municipal and private. It would be unfortunate, if not disastrous, to await the advent of a serious air pollution debacle to do something about it. Barach maintains that the primary attack upon air pollution lies in the development of chemical and engineering methods to cope with the problem. Moreover, government regulation and enforcement, and a vigorous campaign to enlist public support and understanding can help prevent pollution. In the United States, not only the government but industry, engineering and medicine are concerned, and significant strides are being made in establishing regulations for smoke control, sampling, and in setting up long-term statistical studies. Long-term studies on the effects of exposure of normal persons to atmospheres containing low-level concentrations of pollutants have been initiated by federal, state and local groups, as well as by individual scientists.

At present, a division of the U.S. Public Health Service is devoted solely to air pollution. Among its objectives are to determine the effect of air pollution on human health; to assess the effects on the nation's agricultural economy resulting from air pollution damage to animals and crops; to find improved methods for measuring the economic loss from air pollution damage; to find better ways of measuring and identifying air pollutants at their source and in community air; to expand nationwide air pollution monitoring efforts; and to establish and disseminate a comprehensive body of knowledge relating to the technical, legal, economic and administrative aspects of air pollution[14]. Finally, as an example of growing muncipal interest, Chicago has recently enacted a series of comprehensive air pollution ordinances.

Andelman[3] summarizes the problem of air pollution in these words: "A free society requires that its citizens assume a sense of responsibility and the fulfillment of their individual obligations to maintain public health by checking aerial contamination. There is no simple formula to assure success. Air pollution control does not revolve solely about the control of industrial effluents and a reliance on the lazy dictum, 'Let George do it'. Rather, it has to be practiced faithfully by every individual in our communal life if we sincerely want to breathe air that is fit for human consumption."

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DERMATOLOGY AND SYPHILOLOGY

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SOME ASSOCIATED PULMONARY AND CUTANEOUS DISEASES

A REVIEW OF RECENT LITERATURE

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ASSOCIATION of cutaneous and pulmonary manifestations of disease has been known for a long time to internists and dermatologists. A classic example is herpes simplex with pneumonia. However, the frequency and variety of such concomitant lesions have not been fully appreciated. In recent years this awareness has grown and a number of publications have cited the correlation of disease affecting both these systems or in which there is simultaneous but unrelated involvement of them. This presentation reviews some of the cutaneous manifestations occurring in patients with pulmonary disease, and cutaneous disorders in which there may be associated pulmonary (respiratory tract) processes. This is not a pioneering effort since a number of authors have made significant contributions to this subject[32,52,69,122,162].

The following schema gives some idea of the large number of processes which may exhibit at some time during their course, lesions in the skin and respiratory system. We can discuss only some of these to which there have been recent definitive contributions in the literature.

I. HEREDITO-CONGENITAL AND DEVELOPMENTAL ANOMALIES: Familial hereditary telangiectasia (Rendu-Osler-Weber); ataxia telangiectasia (Louis-Bar syndrome); familial autonomic dysfunction (Riley-Day syndrome); porphyria; pseudoxanthoma elasticum; hyalinosis cutis et mucosae (lipoid proteinosis); urticaria pigmentosa (mastocytosis); keratosis follicularis; mucoviscidosis (cystic fibrosis of the pancreas); sickle-cell anemia; Hurler syndrome[117a].

II. INFLAMMATORY PROCESSES: A.

Specific infections and parasitic agents:

1. Bacterial: Staphylococcus; Streptococcus; Pneumococcus; tuberculosis; tularemia; plague; diphtheria; syphilis.
2. Viral: varicella (chickenpox), lymphogranuloma venereum; herpes simplex; rubeola (measles); Behçet's syndrome (viral?).
3. Rickettsial diseases: Rocky Mountain spotted fever; Q fever.
4. Mycotic: actinomycosis; aspergillosis; blastomycosis; coccidioidomycosis; chromoblastomycosis; cryptococcosis; geotrichosis, histoplasmosis, moniliasis (candidiasis); nocardiosis; sporotrichosis.
5. Parasitic: Protozoan: amebiasis, malaria, toxoplasmosis.

   Metazoan: ascariasis, cysticercosis, echinococcosis, filariasis, paragonimiasis, schistosomiasis, visceral larva migrans (creeping eruption).
6. Granulomatous and toxic processes: anthracosis (coal); asbestosis; bagassosis (bagasse); byssinosis (cotton lint); berylliosis; foreign bodies; mustard gas; phosgene, pneumoconiosis (talc and others); siderosis (iron); silicosis (silica); sarcoidosis; stannosis (tin); tobaccosis (tobacco); mineral oil granuloma; chronic pulmonary granulomatosis (Wegener's midline granulomatosis); reticuloendotheliosis (histiocytosis X).

B. *Allergic and Nonspecific.*

Loeffler's syndrome; asthma-eczema complex (atopy); Weber-Christian syndrome.

III. METABOLIC, COLLAGEN, DEGENERATIVE, AND MISCELLANEOUS DISEASES: amyloidosis; eosinophilic granuloma; Gaucher's disease; Hand-Schüller-Christian disease; Letterer-Siwe's disease; extracellular cholesterosis, pulmonary alveolar proteinosis; interstitial fibrosis (Hamman-Rich syndrome); polyarteritis (periarteritis) nodosa; erythema nodosum; rheumatic pneumonitis, scleroderma (progressive systemic sclerosis); systemic lupus erythematosus; dermatomyositis; dys-globulinemias; osteoarthropathy; Plummer-Vinson syndrome.

IV. NEOPLASTIC: mycosis fungoides; angiokeratoma corporis diffusum; leukemia; lymphoma; reticulohistiocytosis; Hodgkin's disease; Kaposi's sarcoma; acanthosis nigricans; arsenical keratoses; Bowen's disease; primary carcinoma (alveolar cell carcinoma; bronchiolar and bronchogenic carcinoma); metastatic lesions from other organs or sites to skin and lungs (carcinoma and sarcoma); multiple myeloma; osteochondroma; hemangio-endothelioma; reticulum cell sarcoma.

HEREDITO-CONGENITAL AND DEVELOPMENTAL ANOMALIES. *Hereditary hemorrhagic telangiectasia.* (*Rendu-Osler-Weber disease.*) This vascular disorder, a hereditary disease of the small blood vessels, is characterized by the formation of multiple, permanent, localized dilatations of the capillaries and venules, which may give rise to apparently spontaneous and often recurrent hemorrhages. This process occurs in the skin and mucous membranes, particularly the face, tongue, and buccal mucosa. Similar telangiectatic and aneurysmal lesions affect the lung and other internal organs. The blood platelet count and the blood calcium levels in this disease are normal, as are also fragility of the red blood cells, and bleeding and coagulation time of the blood. The primary defect appears to be congenital weakness of the blood vessel system[19]. Anemia often is found, but it is a secondary feature because of the frequent active hemorrhages. Epistaxis is the most common symptom. Eigler[55] regarded generalized angiomatosis as a "system disease" of vascular-forming

mesenchyme, and thought that it was parallel with tumor-like disease of the blood forming organs. He stated that the disease did not occur through endothelial branching, but arose from perivascular mesenchymal tissue with slow new vessel formation. Rendu's[128] 1896 report contained the first comprehensive clinical description of the disease manifested by a tendency to epistaxis associated with telangiectasia occurring in families. But even prior to his time it had been noted by others: Chiari[30] in 1883, who reported hemorrhagic telangiectasia in four generations of a family with bleeding from the nose and gums. Other early contributors were: Hutchinson[81], Legg[97], Babington[8], and Sutton[152]. The term "hereditary hemorrhagic telangiectasia" was introduced by Hanes[74] in 1909. By 1932, Goldstein[68] estimated that there were about 600 persons with heredofamilial angiomatosis and hemorrhage reported in the available world medical literature. Madden[107] pointed out that these cases were important, out of proportion to their numbers, by virtue of the fact that they have a higher incidence of fatal terminations. This disorder is not sex-linked in its hereditary aspect, as it occurs in both sexes and is geneticallly transmitted by both sexes. This was carefully and extensively worked out by Cockayne[35] in 1933. Garland and Anning[64a] gave a graphic account of 20 families with Rendu-Osler-Weber disease which they had personally examined. From a thorough review of the literature they were able to account for 244 families reported prior to 1950. These embraced 1,415 affected persons, divided almost equally between the sexes. In another 1950 report[64b] they detailed 3 additional families which had come under their observation and indicated that this entity may not be as rare as was previously supposed, and that it may frequently go undiagnosed. Of 23 families, 22 were from the West Riding of Yorkshire alone. They again emphasized that the defect is inherited as a simple dominant, that epistaxis is usual, and that arteriovenous aneurysms of the lung may be present.

Israel and Gosfield's[86] patient, who had a fatal termination, exhibited hemoptysis from pulmonary arteriovenous fistula. They pointed out the need for Roentgen-ray examination of the chest of all patients with typical cutaneous and mucosal findings of this disorder. They indicated the necessity for surgical intervention when the pulmonary lesion is diagnosed, demonstrated the value of cardiopulmonary function tests in confirming the diagnosis, and reemphasized the ever-present danger of fatal hemoptysis from pulmonary arteriovenous fistula. A patient with classic hereditary hemorrhagic telangiectasia was reported by Bird and Jaques[19] who presented histologic data relevant to the basic vascular defect. The necropsy performed on their patient showed that all major organ systems were affected, and the telangiectasia involved large and small veins primarily, marked by dilatation and tortuosity of these vessels. Large venous channels were found meandering through lung parenchyma, following irregular and serpiginous courses. In every section, extensive ectasia of the pulmonary vessels was evident, and a few arteriovenous shunts were identified. Arterial involvement was inconspicuous. Clinical bleeding seemed to depend more on chance or accessibility of a tissue to trauma than on any predilection of the disease for a particular organ system. Hodgson and his group[78,78a], discussed hereditary hemorrhagic telangiectasia and pulmonary arteriovenous fistula in a large family. Of the 330 descendants of one man afflicted with this disease, approximate-

ly 40% of the individuals studied had telangiectasia and more than 6% had pulmonary arteriovenous fistulas. The fistulas may cause distressing symptoms, even endangering the life of the patient, and these authors also maintain that surgical intervention is indicated for enlarging pulmonary lesions, progressive hemoptysis, and hemothorax.

Ataxia-Telangiectasia (Louis-Bar Syndrome): This syndrome, first described in 1941 by Madame Louis-Bar[104] is characterized by progressive cerebellar ataxia and oculocutaneous telangiectasia. The vascular oculocutaneous aspect of this process was reviewed by Beerman, Kirshbaum and Cowan[13] recently. The Louis-Bar syndrome has been regarded as a neuroectodermal dysplasia or phakomatosis because of the association of the disease of the central nervous system with oculocutaneous abnormalities. However, the pathologic changes of the central nervous system differ from those of the true phakomatoses and more closely resemble those of the heredofamilial degenerative diseases. Boder and Sedgwick[23a], in 1957, reported 7 additional patients with this disorder and noted as less constant features of the syndrome, a familial tendency and frequent pulmonary infection. In 1958, the same authors[23b] reviewed the literature on ataxia-telangiectasia and again stressed its sino-pulmonary disease aspect. Others have also reported the occurrence of sino-pulmonary disease associated with oculocutaneous telangiectasia and ataxia[4,18,29,145,156]. Teller and Millichap[156] described a 9-year-old girl who was admitted to the Mayo Clinic because of chronic refractory disease of the lungs. Their patient was the twenty-ninth case of this syndrome to be published in detail. Ataxia and telangiectasia were associated with choreoathetosis but the disorder of the central nervous system was overshadowed by the prominence of sino-pulmonary disease. The child, ostensibly normal at birth, manifested abnormalities of gait and a persistent, watery nasal discharge before the age of 2 years. At that age, a chronic cough appeared, and pulmonary symptoms predominated until the age of 7. Thereafter, dysfunctions of the central nervous system became more progressive and incapacitating. Roentgenograms of the thorax showed bilateral pneumonitis and partial collapse of the right middle lobe; and the maxillary and ethmoid sinuses were opaque. Telangiectasia were noted in the conjunctivae of both eyes. As yet there seems to be no simple explanation for the relationship among these abnormalities of the eyes, skin, cerebellum, nasal accessory sinuses, and infection of the nasal accessory sinuses and lungs.

Familial Autonomic Dysfunction (Riley-Day Syndrome): The Riley-Day syndrome has been reported in a number of children who present "symptoms so puzzling as to defy exact diagnosis yet so similar as to constitute a clinical entity"[131].

It is characterized by the following fairly constant features: "skin blotching," excessive perspiration, relative indifference to pain, defective lacrimation, drooling, emotional instability, motor incoordination, hyporeflexia, Jewish extraction.

In addition, the following features are frequently found but are not constantly present: frequent pulmonary infection, breath-holding spells in infancy, corneal ulceration, mental retardation, cyclic vomiting, convulsions, frequent unexplained fever, urinary frequency, hypertension.

Riley[130] proposed the term "familial autonomic dysfunction" for this unusual agglomeration of findings. The frequent pulmonary infection is due to aspira-

tion pneumonia caused by either excessive salivation or the cyclic vomiting. In 8 of Riley's cases, death was attributed to aspiration pneumonia.

"Skin blotching" is found in 97% of the cases. The cutaneous symptoms are in the form of erythematous macules of varying size found on the face, neck, extremities, and trunk. Mintzer and Rubin[115] reported on a child in whom these lesions appeared consistently in the same sites when the patient was excited or eating her favorite food. They emphasized that from a dermatologic viewpoint, familiarity with the cutaneous manifestations of this disorder may greatly aid in recognizing and solving an otherwise difficult differential diagnostic problem.

Porphyria. The cutaneous aspects as well as some of the internal manifestations of porphyria have been thoroughly considered in this Journal by Beerman and Pastras[158a]. Acute intermittent porphyria may cause death by producing respiratory failure[44,65,76].

Doll, Bower and Affeldt[48] reported 3 patients with respiratory involvement during recurring episodes of intermittent porphyria who were treated by tracheotomy and mechanical respiratory assistance. All 3 of these patients developed respiratory failure due to paralysis of the respiratory muscles. Acute intermittent porphyria is characterized by exacerbations and remissions. Consequently, these authors believe that if a patient can be tided over the period of respiratory failure by supportive means, he may eventually return to a relatively normal existence. Though such patients are subject to subsequent attacks, they may not produce bulbar or respiratory manifestations.

Pseudoxanthoma Elasticum. The cutaneous and systemic manifestations of pseudoxanthoma elasticum were reviewed recently by Szymanski and Caro[154] as well as by Shaffer, Copelan, and Beerman[142], and by Beerman and Pastras[158b]. Balzer[10] in his original case, noted at necropsy elastic degeneration between the pulmonary alveoli. Miliary opacities in the lung of a 14-year-old boy have been noted by Wolff, Stokes, and Schlesinger[173]. These investigators suggested that degeneration of elastic tissue of the interalveolar septa and of the small pulmonary vessels may lead to multiple small hemorrhages into the alveoli. The Roentgen-ray findings may be produced by deposits of hemosiderin.

Hyalinosis Cutis et Mucosae (Lipoid Proteinosis). Hyalinosis cutis et mucosae is a rare disease in which there is involvement primarily of the skin, but also of mucous membranes extending into the larynx, hence the interest which laryngologists have in this condition as well as dermatologists. In a review by Laymon and Hill[96], these authors feel that hyalinosis cutis et mucosae is unquestionably a genodermatosis since it is commonly familial, and consanguinity of the parents is often found. It is a hereditary disease based upon a Mendelian recessive characteristic depending upon a single gene[158].

The cutaneous lesions of this disorder are yellowish-white, round papules which may be discrete or confluent and are somewhat variable in size. These are usually found on the face, neck, hands, and along the margins of the eyelids where they may have a beaded appearance. Occasionally there may be pustular or bullous lesions followed by crusting and subsequent varioliform scars. Involvement of knees, elbows, hands, and feet is also known. The mucosal lesions are almost invariably present; most commonly affecting the tongue, lips, buccal mucosa, pharynx, and larynx. The tongue is usually firm, with a wooden consistency

and protrusion of the tongue is restricted. The surface is smooth due to atrophy of the papillae. There may be fissuring at the angles of the mouth. All of the structures of the buccal cavity may become involved including the gums, floor of the mouth, soft palate, uvula, and frenulum of the tongue. Dysphagia may become a symptom when there is involvement of the pharynx, and hoarseness may occur when the vocal cords are infiltrated, which in some cases interferes with breathing.

Another term applied to this condition is lipoid proteinosis as it is thought to represent disturbance in both lipid and protein metabolism. Dyslipoidemia or dysproteinemia, or both, have been found associated in some of the cases. Histologically the cutis is found to be permeated by an amorphous structureless substance, probably a galactolipid[174], seen about the small vessels and elsewhere throughout the tissues.

Urticaria Pigmentosa (Mastocytosis). Pulmonary manifestations of the systemic disease associated with urticaria pigmentosa are conspicuous by their rarity[118,136]. Loewenthal, Schen, Berlin, and Wechsler[102], however, noted in the necropsy of their patient that in only a few areas was there considerable infiltration of mast cells in the alveolar septa of the lungs. Collections of mast cells were found in this organ in the connective tissue in relation to the blood vessels, especially the veins. They were also found in the region of the bronchial glands. In one arteriole, there was a subintimal collection of mast cells, protruding into the lumen, almost filling it.

Asboe-Hansen[7] reported the case of an adult patient with pronounced diffuse urticaria pigmentosa and generalized tissue mastocytosis with blood basophilia. He mentioned that there was increased density in the pattern of the right lung and felt that this was due to mastocytosis of this organ as well as similar involvement of other organs of the body. There was the typical urtication of the skin upon slight rubbing.

Keratosis Follicularis and Lung Involvement. Kröger and Müller[93] reported a case of keratosis follicularis (Darier's disease) in which there was involvement of the lungs. They believed this to be the fourth case reported in the literature. This condition first came to their attention in a patient who presented coarse, partly infiltrating and partly circumscribed lesions on roentgenogram of the chest. These lesions did not respond to massive tuberculostatic therapy and on this basis the authors thought that tuberculosis could be excluded. On the other hand, administration of vitamin A was followed by considerable improvement of both the cutaneous lesions and the infiltrating lesions seen in the lungs.

Mucoviscidosis (Cystic Fibrosis of the Pancreas). Cystic fibrosis of the pancreas is defined[46] as a generalized hereditary disease in which there is a dysfunction of exocrine glands. In the fully manifested syndrome there is chronic pulmonary disease, pancreatic deficiency, abnormally high concentration of electrolytes in the sweat, and at times cirrhosis of the liver. A gradation of involvement may occur in some patients, leading to many variations in the clinical picture. Histologic changes are not found in exocrine glands which are nonmucous secreting, such as the eccrine sweat, parotid, and lacrimal glands, but the chemical composition of their secretions is markedly abnormal.

Cystic fibrosis has been found equally in all branches of the white race, but is uncommon in Negroes and has not been described in Mongolians.

The basic defect is genetically determined, and is transmitted as a recessive character. The respiratory involvement in cystic fibrosis has been reviewed by di Sant'Agnese[45]. Chronic pulmonary involvement usually dominates the clinical picture and determines the fate of the patients. Because of the difficulty in removing the abnormal bronchial secretions there can develop severe bronchial obstruction leading to chronic emphysema, to secondary bronchopneumonia, and at times to death due to infection or pulmonary insufficiency. At some time in the course of their disease, pulmonary involvement is present in virtually all patients.

di Sant'Agnese and Andersen[46] mention that they know of only 2 patients who can be said never to have had chronic respiratory involvement; in many of the others, it may be mild and under satisfactory control with antibiotic agents. In addition, they have also reported hemoptysis and spontaneous pneumothorax in a few patients.

The cutaneous findings in cystic fibrosis are manifested by the sweat glands. Almost all patients (99%) show a marked increase of chloride and sodium levels in the sweat. In such patients the sweat glands are unable to conserve salt, although the renal and adrenal cortical function is normal[47]. Massive loss of sodium chloride in the sweat may lead to serious and at times fatal complications in hot weather. This electrolyte abnormality of sweat has not been found in any other disease except adrenal insufficiency. Kulczycki, Mueller, and Shwachman[95], in a study of 266 living patients with cystic fibrosis from age 1½ to 35 years, found respiratory allergy to play a role in nearly 17%. This was based on histories, skin tests, sweat tests, Roentgen-ray examination and repeated clinical evaluation. A control group of patients in this study had respiratory allergies only. The sweat-electrolyte level was markedly elevated in patients with cystic fibrosis and was well within the normal range in patients with respiratory allergy alone. These authors suggested that cystic fibrosis be considered in the differential diagnosis when dealing with recurrent respiratory tract involvement and that one should be aware of the possible coexistence of allergy in patients with confirmed cystic fibrosis.

Sickle-Cell Anemia and Tuberculosis. In a study of the incidence of sickle-cell anemia and tuberculosis, Weiss and Waife[165] demonstrated that Negroes with sickle-cell anemia show a markedly higher incidence of various forms of tuberculosis than do Negroes without sickle-cell anemia. This was based on postmortem data over a span of 13 years (1936 to 1949) at the Philadelphia General Hospital. It would appear that tuberculosis occurs at an earlier age in patients with sickle-cell anemia than in normal persons. In addition, necropsy material showed sickled red cells filling all vessels within all tuberculous lesions, whereas in sections of normal lung tissue in the same patients, there were areas showing vessels containing normally shaped red cells. Weiss and Waife felt that since tuberculous lesions may be affected by oxygen supply and hence by vascular phenomena, it is conceivable that the sickling trait and sickle-cell anemia may be factors in the lack of resistance to tuberculosis exhibited by some Negroes. In another study of this problem, Weiss and Stecher[164] showed that not only was there a relationship between sickle-cell anemia and tuberculosis in the Negro, but that the sickling trait also may be significantly correlated with tuberculosis on a statistical basis. They showed that the

sickling trait is more than twice as common among tuberculous Negroes admitted to a large municipal hospital as it is among nontuberculous Negroes admitted to the same hospital. They also showed that exudative tuberculosis is twice as common among tuberculous Negroes with the sickling trait as it is among tuberculous Negroes without the trait. They concluded that the sickling trait has definite clinical significance and is a factor in the response of some Negroes to tuberculous infection.

VIRAL. *Varicella Pneumonia.* Pneumonia, long known as a complication of varicella, has been reported by a number of authors[26,72,127,160,170]. Krugman, Goodrich and Ward[94], in 1957, reviewed the entire subject in detail. During a 6-month period, primary varicella pneumonia was observed in 10 of 30 adults and in none of 118 children admitted to the hospital for chickenpox. This clinical entity was characterized by a typical varicella eruption followed in 2 to 5 days by moderate to severe respiratory distress associated with cough, dyspnea and tachypnea and frequently with cyanosis and hemoptysis and Roentgen-ray evidence of an extensive generalized nodular infiltrate throughout the lung fields. The illness was severe in 4, moderate in 3, and mild in 3 cases. One patient died. An additional patient died more recently and showed typical pathologic lesions of varicella in the skin, lungs, and liver. Fish[69], in 1960, also noted fatal termination of 4 patients with chickenpox occurring during pregnancy. Each patient died of characteristic diffuse interstitial pneumonia. Fish, in a well documented study of varicella pneumonia, does not believe that there is any special susceptibility to disseminated chickenpox during pregnancy. Mackay and Cairney[106], observed 7 patients in whom chest roentgenograms showed widespread evenly distributed 1 to 3 mm. nodules of calcific density. Calcified nodules may result from pulmonary caseation during varicella pneumonia. In each case the patient had had an attack of chickenpox, usually severe, after the age of 19.

Lymphogranuloma Venereum. Sheldon and his group[143] reported lymphogranuloma venereum in a patient with mediastinal lymphadenopathy and pericarditis. The pulmonary manifestations are not frequent, on the whole, but Jones and Rome[90] had previously cited pulmonary involvement as part of the evidence for systemic nature of this viral disease.

Triple Symptom Complex. Without attempting to attribute them to viral causation or to differentiate or lump the process or processes manifested as mucocutaneous and ocular syndromes (see Beerman, Kirshbaum and Cowan[13]), for purposes of discussion, they will be grouped together at this point. The literature records involvement of all organs by Behçet's syndrome. Diseased lungs have been reported in but few cases. Bonse and Lemke[25] reported the third case with pulmonary involvement. They suggest that when severe recurrent pulmonary hemorrhages occur in an otherwise well patient with Roentgen-ray evidence of diaphragmatic pleurisy, vascular changes and enlarged liver and perihilar manifestation, Behçet's disease be considered in the differential diagnosis. Robinson and McCrumb[132] in their report of 11 cases of the mucocutaneous-ocular syndromes covered the literature fully to 1950, and mentioned respiratory manifestations especially in Reiter's disease but stated that the commonest complications of the group were nasopharyngitis, tracheobronchitis, and pneumonia, but no specific organisms were recovered from the pulmonary lesions. Previously, in

1947, Soll[149] had discussed 20 cases of a process consisting of eruptive fever with involvement of the respiratory tract, conjunctivitis, stomatitis, and balanitis. This group of manifestations was considered interchangeably as erythema multiforme or Stevens-Johnson syndrome.

MYCOTIC. *Deep Mycoses.* It is well known that the deep mycoses of the skin may present concomitant pulmonary manifestations. Martin and Nichols[109] in their compilation on the mycoses stated that lung and cutaneous lesions occur in actinomycosis, nocardiosis (nonspecific pulmonary lesions), cryptococcosis (torulosis), North American blastomycosis, South American blastomycosis (cutaneous and pulmonary manifestations not common), histoplasmosis, coccidioidomycosis, sporotrichosis, candidiasis (moniliasis), aspergillosis geotrichosis (mouth), and mucormycosis. Just as in tuberculosis[12c] erythema nodosum may occur in primary histoplasmosis[100] and coccidioidomycosis[12c,16]. Among 11 patients in 6 years prior to 1960 with erythema nodosum, Little and Steigman[100] found histoplasmosis in 4 and not established in 5. The histoplasmin test was done on only one of these. It yielded negative results. Findings on Roentgen-ray examination of the chest in 4 cases were noncontributory. The fifth patient had no examination. Saslaw and Beman[137] reported another example of erythema nodosum as a manifestation of histoplasmosis.

Moursund and Bowen[116] indicated that mucocutaneous manifestations, especially granulomatous or neoplastic nodular appearing or ulcerative lesions in the buccal cavity, or near the lips, in the nasal cavity, or in the pharynx may be signs of histoplasmosis. Israel and his group[85] found histoplasmosis infrequently as a factor in patients with sarcoidosis studied in Philadelphia. Application of skin and serologic tests, along with mycologic studies to a group of 22 such patients failed to demonstrate evidence of histoplasmosis.

In 28 of 35 patients with North American blastomycosis studied by Abernathy[1], there were disseminated manifestations. Three had only cutaneous lesions and 4 had only pulmonary blastomycosis. Pulmonary manifestations occurred in 27 individuals. Baum and Schwarz[11], in a detailed study, emphasized the concept that blastomycosis of the lungs is the primary form of the disease and all other manifestations stem from the pulmonary lesions. Cutaneous lesions are the most common metastatic manifestations of this fungal disease. It is not a separate form of the disease as was primarily believed. There are, however, exceptional examples of primary cutaneous inoculation so far observed only in laboratory workers. They suggest that blastomycosis be suspected in all chronic pulmonary disorders of granulomatous character which are not tuberculous, histoplasmotic, or of other mycotic origin. Pulmonary involvement formerly considered rare in South American blastomycosis is now known to present a variety of clinical pulmonary signs[63].

PARASITIC. *Pulmonary Larva Migrans (creeping eruption).* In 1945, Wright and Gold[175] reported a series of cases of creeping eruption. In 9 of their cases they noted the development of a transitory pulmonary infiltration associated with eosinophilia. Because of the paucity of clinical signs and symptoms to suggest systemic disease, the cases were reported as those of creeping eruption with Loeffler's syndrome. Later Muhleisen[117] observed a patient in whom he demonstrated pulmonary migration of the causative organism of creeping eruption. Visceral larva migrans caused by ingestion of embry-

onated ova of dog or cat round worms as well as other parasites, was reported in 3 siblings by Heiner and Kevy[77]. They stated that pulmonary infiltration leading to respiratory distress usually with wheezing may be the most prominent manifestation, and may even result in death.

GRANULOMATOUS AND TOXIC PROCESSES. *Berylliosis.* Beryllium disease is now a well-known process with definite pulmonary and cutaneous lesions. In 1951, Beerman[12b] made a detailed comparison of berylliosis with sarcoidosis and found many similarities and predicated a *terrain berilliosique* analagous to the *terrain sarcoidique.* Sneddon[147] has presented a more recent survey of this problem. Curtis[42], one of the earlier workers in berylliosis, noted that of the 32 patients who had chronic pulmonary berylliosis, 5 had no lung symptoms; the abnormality of the lungs was observed in chest roentgenograms. In 3 cases, the pulmonary function tests were normal or could not be interpreted as alveolocapillary block. In 3 cases, both the radiologist and the clinician were indefinite about the interpretation of roentgenographic findings. In one of the 7 cases, the pathologist could not distinguish sarcoidosis from berylliosis (what is more surprising is that he could distinguish any!). In 2 cases with all findings indicating berylliosis, the analysis for beryllium gave negative results. In each of the 32 cases there was a definite history of exposure to dusts and fumes of beryllium compounds. In all cases the patch tests were positive. For diagnosis, the history, histopathologic findings and patch tests are the most valuable. However, the patch test could not stand alone as an absolute pathognomonic sign for the presence of beryllium granulomatosis in the lungs, although a positive test was obtained in all 32 patients with chronic berylliosis.

Sarcoidosis. The pulmonary and cutaneous lesions of sarcoidosis are now a matter of commonplace knowledge. Only brief mention will be made here. Convenient surveys for reference are those of Israel, Beerman and Sones[84]; Israel and Sones[87]; Danbolt[43]; Talbot, Katz and Matthews[155]; Citron[33]; and Löfgren[103]. Goldenberg and Greenspan[66] reported middle-lobe atelectasis due to endobronchial sarcoidosis with hypercalcemia and renal impairment. Arkless and Chodoff[5] likewise made observations on the middle lobe syndrome due to sarcoidosis. The frequency of cutaneous or pulmonary symptoms in sarcoidosis is apparently a variable, depending on whether the patient is seen primarily by a dermatologist or by a pulmonary disease specialist.

Eosinophilic Granuloma; Granulomatous Reticuloendotheliosis (Histiocytosis X). Idiopathic systemic reticuloendotheliosis includes three major conditions: Letterer-Siwe disease, Hand-Schüller-Christian disease, and eosinophilic granuloma. Lichtenstein[99] proposed the name "Histiocytosis X" to designate these three related disease complexes.

The association of eosinophilic granuloma with pulmonary involvement has been reported by a number of authors[2,3,82,163].

Bender and Holtzman[17] reported a case in which there was vegetating papules and nodules with some pustules involving the scalp and papular lesions of the forehead, nose, mouth, chest, lower region of the back, and axillae. About the vulva and in the paranasal and nasolabial folds the papules were grouped, softer, oozing, and vegetating. Only after 4 years of observation did this patient develop dyspnea and this was the first time that roentgenograms revealed peribronchial infiltration in both lower lung

fields. Subsequently, fibrosis and emphysema of both lungs were noted. This patient did not develop exophthalmos; her diabetes insipidus was minimal, and her membranous bone defects were minor.

Williams, Dunnington and Berte[166] reported a series of 5 patients who were found to have abnormal chest roentgenograms and on whom lung biopsies were performed. They also reviewed the literature with respect to those cases where pulmonary lesions were found, in lung biopsies, with the histologic features akin to those described in eosinophilic granuloma of bone. They pointed out that the commonest presenting symptom was cough, with weight loss and dyspnea on exertion next in order, and that other symptoms were far less frequent in occurrence. Approximately 13% of patients had no symptoms at all. They believe that the lesions tend to regress and that clinical improvement, rather than progression to pulmonary insufficiency, is most often seen.

Chronic Pulmonary Granulomatosis (Lethal Midline Granuloma; Wegener's granulomatosis). Wegener's granuloma has recently received more attention[20]. In 1960, McDonald and Edwards[110] proposed that this is a clinico-pathological triad characterized by a necrotizing granulomatous process of the respiratory tract, a generalized vasculitis involving arteries and veins, and focal glomerulitis.

ALLERGIC PROCESSES. *Loeffler's Syndrome.* In 1932, Loeffler[101a] described the syndrome which bears his name and in which transient pulmonary infiltration discoverable by Roentgen-ray examination, as well as blood and sputum eosinophilia, constitute the essential features. Of the more than 200 cases reported since Loeffler's original description a number of the patients have presented cutaneous lesions along with the pulmonary infiltrations[6,62,79,89,151]. Christoforidis and Molnar[31] as well as Bohrod[24] have recently described the pathologic manifestations in the lungs. The causes of this process determined by biopsy and at necropsy include ascariasis[50], poison ivy hyposensitization with 3-pentadecylcatechol[57], gold[53], streptomycin, penicillin[58], antituberculous therapy[172] toxic vapors, paraaminosalicylic acid, nickel sensitivity[151,6] vaginal cream, and arsphenamine. The pathogenesis is variously explained as allergic reaction due to drugs, chemical agents, parasites or fungi, with trapping of eosinophils in the lung[57]. The types of cutaneous lesions reported in association with this lung disease include: dermatitis (nickel sensitivity with positive patch tests to nickel; also arsphenamine dermatitis); nonspecific transient maculopapular eruptions, generalized dermatitis and urticarial lesions.

Much interest is manifested in Loeffler's syndrome in the recent literature[101b]. An example of the association of Loeffler's syndrome and acute nickel dermatitis was reported in 1959 by Arvidsson and Bogg[6]. Sunderman and Sunderman[151] subsequently described the case of a chemical engineer who developed asthma, Loeffler's syndrome and eczematous dermatitis of the hands from exposure to nickel carbonyl. Patch testing demonstrated extreme sensitivity to nickel. Although these are claimed to be the only two examples of transient pulmonary infiltrations and blood eosinophilia occurring in association with sensitivity to metals, cutaneous lesions have occurred in a number of cases of this syndrome[62,79,89]. In the patient described by Tschumy[159] nickel was not demonstrated.

Asthma-Eczema Complex (Atopic dermatitis; generalized neurodermatitis). The allergic basis for pulmonary

disease (asthma) is well known. The "cutaneous counterpart" of this phenomenon, atopic dermatitis, (generalized neurodermatitis) deserves some mention. Schnyder[139] in a study of 112 families of patients with bronchial asthma and rhinitis pollinosa showed that the individual diseases frequently involved the site which is the commonest for that disease in the family. Schnyder and Klunker[140] reviewed the families of 347 unselected patients with atopic diseases. There were 112 patients with constitutional neurodermatitis, 86 of whom had also respiratory involvement, and 235 with bronchial asthma and rhinitis pollinosa. They concluded that bronchial asthma and allergic rhinitis, on the one hand, and constitutional neurodermatitis, on the other, do not behave similarly in their phenotypes. Atopic patients without respiratory system involvement usually carry only the hereditary trait of neurodermatitis. Neurodermatitis patients with conditions of the respiratory tract usually come from families with manifestations of asthma, rhinitis, or neurodermatitis. Lutz and Korting[105] made pulmonary function studies and also concluded that there is a hereditary familial difference in patients with endogenous eczema, implying that there are families with endogenous eczema with or without involvement of the respiratory tract. There are thus two distinct groups of atopic dermatitis patients, namely those with a hereditary trait for atopic dermatitis, and those with a hereditary trait for atopic dermatitis and respiratory allergies. A group of 43 children with infantile eczema were studied from both the skin and respiratory viewpoint by Burrows and Penman[27], in an attempt to establish prognosis of the eczema-asthma syndrome. Twenty children were studied intensively (13 males, 7 females). This small group of subjects showed no significant difference between the sexes in the severity of skin or pulmonary manifestations of the syndrome.

Weber-Christian Syndrome. This disease of the adipose tissue was discussed fully in this Journal by Beerman[124]. Pulmonary manifestations are not a prominent feature of this process although Dorfman[49] presented a typical example of the subcutaneous nodules in a patient who also had bilateral pulmonary hilar enlargement with subsequent remission. Miller and Kritzler's[112] patient who apparently had changes of the fat at necropsy, died of cachexia, fat embolism and pneumonia. The latter was obviously not a part of the disease *per se*.

METABOLIC, COLLAGEN, DEGENERATIVE AND MISCELLANEOUS DISEASES. *Dyslipidoses (Lipid diseases).* Lung lesions are not frequent clinical manifestations of the dyslipidoses[61,157]. Occasional pulmonary involvement in one or another type may occur mainly as a coincidence. The lungs may be affected in Niemann-Pick's disease, Letterer-Siwe's disease and gargoylism or eosinophilic granuloma. In the latter there may be cough, chest pain, and hemoptysis (see section on granulomas). Sobel and Pollock[148] have seen a patient with extracellular cholesterosis and pulmonary involvement consisting of bilateral productive infiltrations which were partly confluent in the first right intercostal space. Several small nodular shadows were seen in both upper lung fields. Necropsy in 1950[124] revealed in addition to the changes previously documented, bronchiectasis with cavity formation and emphysema, as well as lesions in the liver, gallbladder, pancreas and kidneys which were interpreted as periarteritis nodosa.

Periarteritis nodosa (Polyarteritis). Some mention of periarteritis has been

made in an earlier presentation[14]. In spite of enormous interest and work there is still considerable confusion in the area of the vasculitides, cutaneous and otherwise. No further attempt will be made to review the subject in detail. The pulmonary lesions were studied by Sweeney and Baggenstoss[153] who found that, contrary to the belief that pulmonary lesions are uncommon, necropsy disclosed characteristic lesions of the vessels of the bronchi and lungs in 8 of 28 cases of periarteritis nodosa in patients who were observed at the Mayo Clinic. Their findings were in keeping with the incidence of 25% and 29% reported earlier by Harris, Lynch, and O'Hare[75] and Spiegel[150] respectively. The pulmonary lesions consisted of perivascular pneumonia, granuloma and scars. Bohrod[24] made a detailed review of allergic arteritis and polyarteritis nodosa. He feels that polyarteritis nodosa looms large in any discussion of both allergic and collagen diseases, because of all the admitted collagen diseases it has the closest relation to antigen-antibody reaction and it therefore forms a kind of bridge which links the two conditions together. He feels the relative immunity of the lung in classical polyarteritis nodosa is the result of the normal low intrapulmonary blood pressure and it is likely to be lost when for any reason the intrapulmonary blood pressure is increased.

Collagen Diseases. Clough[34] in an editorial has reaffirmed the increasing awareness among the medical profession of the so-called collagen diseases in recent years. Diagnosis has been made or suspected with increasing frequency, and it has been noted that these diseases are all benefited, if not cured, by the administration of corticotropin or cortisone-like drugs. There is also widespread belief that they are due to allergic reactions of some sort.

Klemperer, Pollack and Baehr[92] applied the term collagen disease to disseminated lupus erythematosus, diffuse scleroderma, and later to dermatomyositis. They implied that these diseases were not restricted to any specific organ but were manifestations of widespread injury to a diffusely distributed tissue, the connective tissue. The term has since been expanded to embrace other diseases with similar findings in connective tissue, namely rheumatic fever, rheumatoid arthritis, serum sickness, and periarteritis nodosa. In the collagen diseases the first change is a mucoid degeneration (myxomatous swelling) of the ground substance followed by a fibrinoid degeneration with fragmentation of fibers and deposition of highly refractile material. This is associated with infiltration of leukocytes, plasma cells and lymphocytes and by proliferation of fibroblasts, leading eventually to sclerosis.

Systemic Lupus Erythematosus. In a review by Ross and Wells[133] the earliest description of the cutaneous lesions has been attributed to Biett who, in 1828, applied the term "érythème centrifuge" to them. In 1851, Cazenave, a pupil of Biett, devised the term "lupus erythematodes" and believed it to be related to lupus vulgaris. The typical skin lesions are too well known to require description in this presentation, but in addition to lesions of the "V-area" of the neck and the facial skin ("butterfly" distribution across the bridge of the nose and cheeks), there may be ecchymoses, petechiae, pigmentary changes, alopecia and mucous membrane lesions[141]. Any of these findings in a patient who is otherwise obscurely ill should at once arouse suspicion of lupus erythematosus.

In 1904, Osler[120] emphasized the visceral manifestations and placed the disease in the field of general medicine

rather than dermatology exclusively. He felt that the recurring cutaneous lesions, the pleuropneumonia and other findings in this disease were due to the same noxae.

With regard to the pulmonary manifestations of this condition, pleuritis and pneumonitis are most commonly found. In a review of the Roentgenray findings in systemic lupus erythematosus, Gould and Daves[70b] noted that a well defined roentgenographic pattern of the various manifestations can be grouped in a six point constellation consisting of: (1) pleuritis, (2) pneumonitis, (3) carditis, (4) splenitis, (5) enteritis, and (6) arthritis. They also noted that the findings must be differentiated from viral pneumonia, tuberculosis, fungal infection, sickle cell anemia, and many other conditions which may present features similar to that found in systemic lupus erythematosus. The roentgenographic pattern of pulmonary involvement is usually described as patchy lesions resembling bronchopneumonia, atelectasis, infarction, and even gangrene. According to these authors there are two main forms of pneumonitis: the acute patch which is ill-defined in both outline and substance, and the chronic horizontal atelectatic plaque. Both forms occur most frequently at the lung bases and there is a tendency toward bilateral involvement although not as marked as with the pleuritis. If the ill defined patch is followed over a period of time one may see it change to the horizontal atelectatic plaque or band.

In another report on the roentgenologic findings in systemic lupus erythematosus, Gould and Daves[70a] again emphasized the role of pleuritis in this disease and noted that it was the most common finding. Pleuritis was recognizable on the chest roentgenogram as a shaggy thickening of the pleural surface. The other qualities of the pleuritis in their opinion reflected the fibrinous matter of the reaction. This was supported by the regularity with which fibrinous pleuritis appeared in the necropsy reports. In most cases the pleural reaction was minimal, rarely massive. The incidence of pleural reaction was about 74%, with bilateral pleural involvement occurring in 51% of cases. The involvement in the lung parenchyma was also described and was found in 50 of the 100 patients examined. Again most of the findings were present in the lower lobes. The literature on pleuritis in systemic lupus erythematosus, and its importance as an early manifestation in diagnosis was reviewed by Winslow, Ploss and Loitman[169]. Their interest in the problem was stimulated by two similar cases of relatively isolated pleuritis in young women who had negative tuberculin tests and repeatedly positive lupus erythematosus cell preparations. They also reviewed the charts and studied the roentgenograms of 77 additional patients with systemic lupus erythematosus at Montefiore and New York Hospitals. They concluded that pleuritis with and without effusion is common in this disease and that it is often an early sign of involvement. Indeed, in several of their cases it appeared as an isolated first sign. They therefore suggested that individuals with unexplained pleuritis be promptly studied for systemic lupus erythematosus as well as for tuberculosis or neoplasm.

Israel[83] considering the pulmonary manifestations of disseminated lupus erythematosus found that there was some roentgenological or pathological evidence of pulmonary or pleural disease in 20 of 22 patients examined. This involvement consisted variously of pneumonitis, diffuse pulmonary infiltration, bronchopneumonia, pulmonary edema, pleuritis, lobar pneumo-

nia, and pleurisy with effusion. He felt that pulmonary involvement is so common in disseminated lupus erythematosus that it cannot be considered coincidental and that in pulmonary or pleural disease of obscure cause, lupus erythematosus requires consideration. Indeed, disseminated lupus erythematosus may occasionally present predominantly respiratory manifestations. He agreed with the previous authors that respiratory involvement may often be found at the onset of the disease and that a nonspecific pneumonitis may occur frequently during the course of the disease as well as a terminal event. Purnell, Bagenstoss, and Olsen[125] reviewed the pulmonary lesions in disseminated lupus erythematosus in 54 patients on whom they had necropsy data. They found that some form of pulmonary pathology was present in virtually all cases, with terminal bronchopneumonia as the most common finding, occurring in slightly more than 75% of their series. They were able to confirm the earlier findings of Baggenstoss[9] who observed a peculiar basophilic interstitial mucinous edema in association with interstitial pneumonitis and alveolar hemorrhage in a patient who died of disseminated lupus erythematosus.

Several other reports of disseminated lupus erythematosus in which pulmonary involvement is mentioned are those of Costello, Havrilla and Bouquette[36], McCombs and Patterson[111], and Jessar, Lamont-Havers, Bulgrin, Dubois and Jacobson[25a] and Ragan[88]. An unusual case of acute lupus erythematosus with laryngeal involvement is described by Scarpelli, McCoy and Scott[138], in which the patient died as the result of severe laryngeal edema secondary to involvement by lupus erythematosus. At necropsy the larynx showed marked edema of the cuneiform tubercles and the arytenoepiglottic folds. Cassidy and Kennedy[28] observed an example of systemic lupus erythematosus in a 16-year-old boy presenting symptoms of bronchiectasis. The diagnosis of the patient's underlying systemic disease was complicated by a nonspecific bronchopneumonia, with partial atelectasis at the base of the left lung, and the production of an enormous amount of sputum.

Generalized Scleroderma (Progressive Systemic Sclerosis). The visceral manifestations of scleroderma have been previously reviewed in this Journal by one of us[12a] in 1948. At that time extensive reference to the pulmonary lesions was made. The sclerotic changes of the skin are well known and the disorder is also manifested in the connective tissues of various organs and systems (muscles, bones, joints, tendons, fascia, internal viscera, endocrine glands, and nervous system) in addition to the skin. The pulmonary changes have been reported to be mainly those of diffuse pulmonary fibrosis, interstitial pneumonia, and cystic sclerosis of the lung. Varying degrees of dyspnea are therefore the usual symptomatology: hoarseness and pulmonary infections are also encountered.

Rothman and Walker[134] in their report mentioned that the roentgenogram of the chest shows a peculiar diffuse granular, mottled or networklike shadow most marked at the bases and usually sparing the apices of the lung. Bronchography with iodized oil usually reveals a normal bronchial tree. In advanced cases there may be pulmonary emphysema. In a report by Beigelman, Goldner and Bayles[16], the roentgenograms in 7 of their 9 patients revealed definite pulmonary abnormalities, chiefly nodular and linear streaking at the bases. Shuford, Seaman and Goldman[144] reported on 37 patients in whom the clinical diagnosis of scleroderma had been established. The roent-

genographic findings in 5 of these patients were strikingly similar and consisted of a diffuse linear interstitial infiltration, more marked in the lower half of both lung fields. They pointed out that knowledge of the pulmonary changes occurring in scleroderma is of particular importance since they may precede the onset of the characteristic skin lesions. Scleroderma of the lungs should be considered in the differential diagnosis of obscure causes of pulmonary fibrosis.

Mahrer, Evans, and Steinberg[108] reported on the relation of pulmonary changes to esophageal disease in scleroderma. They detailed 41 cases from the literature and added their own experience with 16 patients. They found the severity of the pulmonary disease to vary from no symptoms to severe dyspnea and cyanosis. The majority had exertional dyspnea. Cough was present in some patients but was not very common. There were recurrent attacks of pneumonitis and pleurisy in several of the patients. The most common physical finding was rales at the lung bases. They noted that the roentgenographic changes were mostly mottling of the lung parenchyma consistent with pulmonary fibrosis and usually occurring at the bases. In several patients there was a "honeycomb appearance" produced by cysts of various sizes at the bases. These authors found that esophageal involvement occurred in 56% of the cases with pulmonary lesions described in the literature and that 69% of the patients in their own series had similar involvement. They pointed out that cor pulmonale is a late manifestation when there is progressive fibrosis of the lung and that the pathologic changes consist of fibrosis, with half of the cases demonstrating cystic bronchiolar hyperplasia.

Dowling[51], in the British Journal of Dermatology, cited clinical and radiologic findings essentially similar to those noted by others, and in a patient under investigation at St. Thomas Hospital, the early changes of scleroderma were examined in a portion of lung removed by biopsy. The microscopic findings consisted of: (1) thickening of the alveolar walls with tortuosity of capillaries, (2) partial collapse and focal slight emphysema, (3) patchy fibrosis, (4) degeneration of small arteries some of which were almost obliterated by intimal hyperplasia, (5) phagocytosis of blood pigment in alveoli. Piper and Helwig[121] found an incidence of 90% of pulmonary lesions in their series of 31 cases. The lungs were examined grossly and microscopically in each of these individuals. In 29 of the cases there was fibrosis, usually interstitial, which rendered the alveolar septa quite thick, In some instances the alveolar septa had ruptured with the formation of small to large cystic spaces surrounded by fibrous tissue. This fibrous tissue ranged from a dense, rather acellular type, to a looser cellular stroma which was infiltrated with inflammatory cells.

Opie[119] noted that involvement of the hilar, bronchial, and mediastinal lymph nodes, so frequently found in sarcoidosis, is not reported as being associated with scleroderma. Cystic pulmosclerosis is the cause of "honeycombing" of the lungs in scleroderma. He also pointed out that respiratory reserve and function may be limited even in the absence of pulmosclerosis by purely mechanical factors such as sclerosis in the overlying skin, calcinosis of the soft tissues, fibrous pleurisy, and mediastinitis as well as the passive congestion consequent on scleroderma heart disease. Pulmonary hypertension which may be due to obstruction of pulmonary vessels, and anoxia associated with chronic lung disease

are likely to occur in generalized scleroderma. The diagnosis of pulmonary hypertension in a patient with systemic scleroderma, therefore, requires careful clinical, electrocardiographic, and radiological evaluation.

Miller, Fowler, and Helmholz[113] reported a series of 22 patients with scleroderma who underwent tests of pulmonary function. They were classified according to roentgenographic evidence of the severity of pulmonary fibrosis in 4 groups as follows: 1) no fibrosis, 2) mild localized fibrosis, 3) moderate generalized fibrosis, and 4) severe generalized fibrosis. They found that the total capacity of the lungs was progressively decreased as the pulmonary fibrosis became more severe and more generalized. The vital capacity was reduced in all groups but especially in the fourth group. The residual volume was reduced only in those patients with generalized pulmonary fibrosis. Hypoxemia was not observed in patients without signs of fibrosis except in 2 emphysematous individuals. Hypoxemia with exercise occurred in most of the patients with generalized fibrosis.

Dermatomyositis. Dermatomyositis, another of the collagen diseases, presents some similarities to scleroderma and systemic lupus erythematosus, but differs from the other diseases in this group in that the lungs have rarely been found involved in dermatomyositis as part of the basic disease. Mills and Mathews[114] reported on a 52-year-old woman who presented signs and symptoms consistent with dermatomyositis and in whom the roentgenograms of the chest showed widespread interstitial infiltrations within the parenchyma of the right lung and, to a lesser extent, of the left lower lobe. At necropsy, the lung tissue was found to be markedly altered, showing extensive areas of collapse, interstitial fibrosis, and a chronic inflammatory cell infiltration. Some areas exhibited dilated bronchioles with extensive degeneration of the bronchial epithelium. Elsewhere the lung tissue showed congestion and edema. The second case of dermatomyositis with pulmonary lesions was reported by Goldfischer and Rubin[67]. The patient, a 62-year-old white man, followed essentially the course of other patients with dermatomyositis in that there was wasting of the temporal and masseter muscles, weakness of all cervical muscles, marked wasting of the muscles at the shoulder girdles and glutei, weakness in the shoulders and marked weakness of the pelvic girdle musculature. The L.E. cell preparations yielded negative results. The PPD skin tests in this patient were nonreactive in both strengths. A biopsy specimen of the skin and muscle confirmed the other findings. The roentgenograms of the chest in the initial stages of the disease showed bilateral patchy infiltrations with conglomerate areas in the right mid-lung region. Later the infiltrations became more diffuse, stringy, and interstitial, similar to the lesions noted in the other collagen diseases. The lung biopsy and subsequent necropsy specimens revealed thickening of alveolar septa and increase in perivascular and peribronchial connective tissues, as well as diffuse bronchiolectasis and emphysematous "honeycombing."

Association of dermatomyositis and malignancy was previously discussed in this Journal by Beerman[12e]. New material on this subject is presented in the section on tumors.

TUMORS (NEOPLASTIC DISEASES). In a general review of dermatoses associated with malignant internal tumors, Helen Curth[39] presented the various dermatologic manifestations and the likely types of tumor which can occur with each, as well as the significance

of these associations. This subject was also discussed in these pages by Beerman[12c].

Pachydermoperiostosis, which consists of thickening of the skin with accentuation of the folds, including cutis verticis gyrata, macroglossia and enlargement of extremities and joints with clubbing of fingers occurs almost exclusively in men over 40 years of age and is often associated with bronchogenic carcinoma.

Malignant acanthosis nigricans is associated with internal malignant tumor. The hyperpigmented verrucous lesions of the acanthosis usually occur in body folds, about the nipples, umbilicus and peri-anal areas. Occasionally the mucous membranes, palms and soles may be affected. Among the types of malignancy associated with acanthosis nigricans there may be adenocarcinoma of the lung. According to Curth and Aschner[40], the dermatosis may begin before, at the time of, or after manifestation of the internal cancer. It usually follows a course concomitant with the propagation of the cancer, but may show temporary regression after operation or irradiation of the tumor. It apparently does not seem to follow genetically determined lines. In 26 patients whom they reviewed, 3 had primary bronchial malignancy and one had cancer in a hilar lymph node, but the primary site was unknown.

Dermatomyositis is also associated with malignancy of the lung in men more often than in women. (Dermatomyositis and scleroderma associated with internal malignancy are reviewed later in this section.)

Erythema multiforme may occasionally be the cutaneous expression of bronchogenic carcinoma. *Erythema gyratum repens*, which occurs in irregular wavy bands on the trunk, neck, and extremities, has a peculiar serpiginous, constantly changing outline, and may indicate the presence of anaplastic "oat-cell" carcinoma of the lung. It has been speculated that the cutaneous eruption is caused by allergy to a carcinotoxin.

Bowen's disease. Bowen's disease and its relationship to systemic cancer was studied by Graham and Helwig[71]. They found primary malignancy of the lung in 6 of 35 patients, and a total of 13 patients (including the previous 6 with primary lesions) who had pulmonary metastases.

Erythroplasia. Witham, Garretts, Levine, and Jarrett[171] reported a case of fatal metastasizing erythroplasia in which the lung was involved. Erythroplasia, first described by Queyrat[126], in 1911, has been regarded as precancerous (actually Bowen's disease). Subsequently it usually develops into an invasive prickle-cell epithelioma. In the patient described by Witham's group, the lesion was originally an erythematous discoid plaque of the left loin. Subsequently the tumor spread into the groins as cancer en cuirass. Three weeks before death, the patient developed a right pleural effusion which contained cells highly suggestive of carcinoma. This was confirmed at postmortem examination when the visceral pleurae of both lungs and the periphery of the right upper lobe were found to be involved.

Basal cell epithelioma. Though it is a relatively frequent cutaneous tumor, the basal cell epithelioma rarely metastasizes, even to nearby lymph nodes. Therefore, cases in which there are metastases to distant organs are distinctly unusual. Small and Hankins[146] cited 9 such cases in the literature and added 2 cases of their own in which many tumor nodules were found in the lungs. On microscopic examination, these resembled primarily basal cell carcinoma. The original sites of the basal cell epithelioma in both patients

was the external ear. Huntington and Levan[80] also reported a case in which basal cell carcinoma metastasized from skin to lung. The patient was a white man who died at the age of 66 years with a huge exophytic tumor of the face. The lesion had arisen near the nose and was present for approximately 23 years before the patient's death. Typical adenocystic basal cell carcinoma was demonstrated in the biopsy specimen. Terminally there was destruction of the superior and nasal portion of the orbit, and the postmortem examination revealed numerous nodular tumor masses in the lungs, histologically identical with the tumor of the face.

Bronchogenic carcinoma and Cushing's syndrome. Lewis, Searle, and Jordan[98] reviewed the literature on Cushing's syndrome in association with bronchogenic carcinoma and reported an additional case of their own. Up to the time of their study, there had been 7 cases of this relationship reported in the literature. In all instances the lung cancer was of the "oat-cell" or reserve cell type. Six of the 8 patients were males. Seven of the patients had hyperplastic adrenal glands. Metastases to the adrenal were demonstrable in 5 of the 8 cases. This combination of Cushing's syndrome and bronchogenic carcinoma is not considered by Searle and his co-workers as a chance association.

Mycosis fungoides. Pulmonary manifestations of mycosis fungoides were noted in 4 patients by Bluefarb and Steinberg[22]. As is well known, mycosis fungoides is a disease of the reticuloendothelial system, with its manifestations primarily in the skin although there are frequent visceral manifestations. In Bluefarb and Steinberg's cases, the pulmonary infiltrations were found roentgenographically. Pathologic (necropsy) confirmation was established in 3 patients. In the fourth patient, the pulmonary lesions seen in the roentgenogram cleared following treatment with nitrogen mustard and radioactive phosphorus. It was pointed out that the pulmonary findings roentgenographically resembled those of Boeck's sarcoid closely, and that in both diseases there is a positive anergy to the tuberculin test.

Kaposi's sarcoma. Greenstein and Conston[73] reported a case of coexistent Hodgkin's disease and Kaposi's sarcoma. In this patient, small pulmonary infiltrations of Hodgkin's lesions were confirmed on histologic examination of the necropsy material. There were also findings of cutaneous angio-endothelioma (Kaposi's sarcoma) with lymph node and pulmonary metastases. Of the 50 patients with Kaposi's sarcoma analyzed by Cox and Helwig[37] there was involvement of the lungs in 6. The pulmonary involvement was characterized by multiple lesions located predominantly around blood vessels and bronchioles and beneath the pleurae. Histologically, the characteristic spindle-shaped cells intimately associated with vascular slits were found. Bluefarb[21] pointed out that nearly all portions of the respiratory tract except the nasal cavity have been involved by tumor nodules of Kaposi's sarcoma. He cites a number of authors who have described patients with involvement of the pleural surfaces of the lungs, the pulmonary parenchyma and the hilus of each lung as well as the mediastinum and retroperitoneal areas. Lesions of Kaposi's sarcoma have also been described in the bronchi, the larynx and the trachea. Ervin Epstein[56] discussing the extracutaneous manifestations of Kaposi's sarcoma, considers the process to be a systemic lymphoblastoma. Among 35 patients in whom there was visceral involvement, the respiratory system includin

the trachea, bronchi, pleura and parenchyma of the lung was affected in 8 instances. In those patients studied roentgenographically there were multiple lesions, occasionally simulating pneumonia, tuberculosis or tumor. Cough, hemoptysis and pleurisy were the presenting symptoms in some of the patients.

Hemangioendothelioma. Hemangioendothelioma of the skin with metastases to the lung as well as lymph nodes and the liver was reported by Weidman[161]. The patient, a woman of 71 years, first noted a solid tumor on the skin of her face. This was histologically a hemangioendothelioma. She lived only 11 months after the diagnosis was established and at necropsy the lung was found to be extensively invaded by tumor cells.

Angiokeratoma corporis diffusum. Angiokeratoma corporis diffusum, originally considered a vascular dermatosis only, is now recognized as a systemic process. The clinical and other aspects of this disease were reviewed in this Journal in an earlier study[15b]. Other convenient compilations are those by Ruiter[135] and his colleague Pompen[123], an early student of angiokeratoma, and that by Duperrat[54]. Although primarily a vascular disease, Pompen and Ruiter[123] found remarkable and unexplained lesions in the lungs of the first of their 2 patients. The bronchial tubes were lined with taller than normal epitheium. On the lumen side there was a broad border of somewhat vacuolated pale protoplasm. The alveoli were partly collapsed, partly dilated. There was a precipitate in many of the alveoli. There was no inflammation in the alveoli but there was some yellowish pigment in addition to the anthracotic pigment. The blood vessels of the lung were also involved. A recent report is that of Curry and Fleisher[38], who recorded the fifth case of this entity in the United States. In addition to presenting the detailed findings in their patient, they reviewed the extant American literature on this disease, the first case having been reported in 1955[59].

Scleroderma and carcinoma of the lung. The association of carcinoma and scleroderma has been repeatedly reported. Zatuchni, Campbell and Zarafonetis[177] reported 3 cases of terminal bronchiolar ("alveolar cell") carcinoma in patients with scleroderma. These authors believed that there was no previous reported case of scleroderma associated with lung cancer in the literature. Progressive systemic sclerosis (scleroderma) associated with cancer of the lung was also observed by Jonsson and Houser[91]. The pulmonary tumor was composed of a cellular undifferentiated bronchogenic adenocarcinoma. Cancer of the lung in progressive systemic sclerosis (scleroderma) was encountered in 2 patients by Richards and Milne[129]. They believed that the pulmonary changes of progressive systemic sclerosis may predispose to the development of cancer of the lung.

Dermatomyositis and carcinoma of the lung. Malignant lesions associated with dermatomyositis have been frequently reported in the literature[12c,41]. Dowling[51] reviewed 31 such cases in the literature. Williams[167] reported on 590 patients with dermatomyositis which he gathered in the literature. Of this number 92 had an associated malignant tumor, of which 14 were in the lung.

Carcinoid. Zarafonetis, Lorber and Hanson[176] reported the association of functioning carcinoid syndrome and scleroderma. At necropsy there were metastases to the lung as well as to other internal viscera. Beerman and Pastras[15b] have also noted that pulmonary involvement occurs in the carcinoid syndrome.

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PROCEEDINGS OF

The Physiological Society of Philadelphia

SESSION OF MARCH 21, 1961

SEMINAR ON PHYSIOLOGY OF DIGESTIVE SYSTEM

Mechanisms Concerned in the Control of Gastric Motor Function. STANLEY H. LORBER, M.D. (Fels Research Institute, Temple University School of Medicine). Gastric motor function is affected by many factors. Among the more important regulatory influences are the changes in blood glucose levels, gastric secretion (as it affects duodenal pH) and the quantity and properties of ingested material. The latter exert some effects directly on the stomach and others on the duodenal mechanism which in turn effects gastric motility. Previous studies have shown that inhibitory influences are initiated in the duodenum in response to foodstuffs, hydrochloric acid, hypertonic solutions or distention and result from neural and hormonal stimulation. Our present investigations have been undertaken to learn more about these mechanisms.

Four dogs, each equipped with a gastric fistula and Heidenhain pouch, were used. Fluoroscopic observation was employed for control of duodenal intubation. Test substances were introduced into the duodenum at the rate of 2 ml. per minute for a maximum of 10 minutes. In studies with distention, a balloon was attached to the tube. Balloons were used to record motor activity simultaneously from the stomach and Heidenhain pouch. In other studies, Insulin 0.25 unit per kilogram was administered intravenously. Five percent glucose was administered intravenously at rates of 4,8, or 12 ml. per minute.

The instillation of 2 to 10 ml. of olive oil produced inhibition of motor activity in the stomach. Olive oil, in doses of 4 to 10 ml., also produced inhibition of motor activity in the Heidenhain pouch but the latent period in the pouch was 3.4 minutes longer. Two milliliters of olive oil depressed but did not completely inhibit pouch motor activity. Hypertonic solutions of glucose and saline and an isotonic solution of HCl were weaker inhibitors of motor activity. Twenty milliliters of these solutions depressed but did not inhibit motor activity of the stomach in all experiments. Their effects on the Heidenhain pouch were even weaker. Hypertonic solutions and HCl had shorter latent periods for inhibition of stomach and pouch than those observed after olive oil instillation but, as with olive oil, gastric inhibitory effects preceded those in the Heidenhain pouch. Distention of a balloon in the duodenum sufficient to inhibit gastric motor function only depressed pouch activity. Balloon distention was a painful stimulus and its inhibitory effects were prompt.

Insulin hypoglycemia stimulated gastric motor activity and depressed pouch activity. These effects could be reversed by administering glucose intravenously. Intravenous glucose, administered alone, completely inhibited gastric motor function in all experiments but only depressed pouch motility. The significance of these observations with regard to the role of neural and hormonal mechanisms were discussed.

Role of the Bile Ductules in Bile Formation. HANS POPPER, M.D. (Department of Pathology, The Mount Sinai Hospital, New York). The bile ductules as the link between the bile canaliculi lined by liver cells and the bile ducts in the portal tracts are the only epithelial structures in the liver surrounded by a basement membrane. They proliferate in various hepatic diseases when they are usually surrounded by inflammatory cells (ductular cell reaction). Their luminal membrane is thrown into microvilli with an internal structure as seen under the electron microscope. They resemble the microvilli of the bile canaliculi which latter are stunted or obliterated in both intrahepatic and extrahepatic cholestasis (Schaffner). Since both types of cholestasis are associated with inspissation of bile, the hepatocellular biliary microvilli might influence hydration of the bile. In experimentally produced excessive proliferation of the bile ductules as in chronic ethionine intoxicaton, the volume of bile is increased up to four times the normal with relative and absolute reduction of excretion of solids, bile acids and bile pigments. In liver cell injury without bile ductular proliferation as in carbon tetrachloride or acute ethionine intoxication, bile flow is normal but concentration of solids reduced (Goldfarb and Singer). It appears that the microvilli of the bile ductules secrete a fluid free of biliary constituents but containing electrolytes as reflected in chemical analyses possibly in analogy to those of the liver cells. Hydrocholeresis is also found in chronic proliferation of bile ductules produced by alpha-naphthyl-thiocyanate which initially produces acute biliary obstruction. Under abnormal circumstances lumen and epithelium of bile ductules contains material, presumably of mucopolysaccharide character, to which binding antibodies are found in the serum gamma globulin of patients with liver diseases (Paronetto). Since immunocytochemical analysis proves furthermore that mesenchymal cells around proliferated bile ductules might form gamma globulin, presumably an antibody, the possibility arises that an antigen/antibody product might act as a local tissue irritant. Activation of the mesenchymal cells around bile ductules is also reflected in the frequently seen periductular fibrogenesis as well as in fiber destruction in this location (Hutterer and Rubin). The role of the ductular cell reaction, functionally characterized by hydrocholeresis, in perpetuating liver disease and the nature of the irritant requires further study.

Twenty-four Hour Collections of Fasting Gastric Content in Monkeys. F. P. BROOKS, M.D., F. ATTINGER, A.B., and G. BJOVEDT, V.M.D. (Departments of Physiology and Animal Medicine, University of Pennsylvania). Gastric content was collected at hourly intervals for 24 hours from 4 unrestrained spider monkeys and 2 macaques. An L-shaped plastic fitting was screwed into a chronic gastric fistula and connected by rubber tubing to a plastic bottle. The bottle fitted into a pocket on the inside of a cloth suit tailored to fit the particular monkey. A piece of polyethylene tubing was inserted to the bottom of the bottle and positioned to emerge at the nape of the animal's neck. This was occluded with a plug between collections which were made with a syringe. Between collections the monkey was free as usual in its cage. The pH of collections from the two macaques remained above 3.0 throughout the 24 hours. Three of the spider monkeys showed pHs in the range 1 to 2 during the day and 5 to 7 at night. In 2, the pH fell again to

1 to 2 the next morning. The mean volumes in ml. per hr. of specimens with pH above 3.5 were 2.4 to 4.8, while in those with a pH less than 3.5 they were 4.1 to 6.5. Comparing specimens in day and night periods on the basis of the highest chloride concentrations, the pH of the day specimens was 1.1 to 1.3, Na 20 to 60 mEq. per L., K 13.4 to 20 mEq. per L., and Cl 129 to 147 mEq. per L. For the night specimens the corresponding values were pH 6 to 7.3, Na 108 to 148 mEq. per L., K 13.6 to 30 mEq. per L., and Cl 110 to 152 mEq. per L. These results confirm earlier reports of absence of "free" acid in fasting gastric content of macaques, and establish that in the spider monkey secretion of acid gastric content is intermittent.

BOOK REVIEWS AND NOTICES

RECENT ADVANCES IN BIOCHEMISTRY. By T. W. GOODWIN, D.Sc., F.R.I.C., University College of Wales. 4th ed. Pp. 301; 88 ills. Boston: Little, Brown and Co., 1960. Price, $11.50.

THIS fourth edition of a series, previous editions of which were published in 1926, 1928 and 1931 includes necessarily a rather arbitrary selection of topics considering the formidable accumulation of biochemical information since the last edition.

The fields selected for discussion are (1) electron transport and oxidative phosphorylation, and biochemical energetics; (2) carbon dioxide fixation, important in animals as well as in plants; (3-7) chemistry and bio-synthesis of phospholipids, aromatic ring systems, heterocyclic ring systems, nucleic acids, and terpenes; and (8) regulation of cell metabolism.

The author has attempted "to bridge the gap between general textbooks and specialized review articles" for "senior under-graduates and junior research workers" and covers most of the literature in the fields of discussion up to the end of 1959. To a considerable degree he has succeeded in this task and the text is quite readable to the non-expert in the field. He has also included reference bibliography in profusion. It is to be hoped that the 5th edition will not be awaited for so long a time as this present volume.

J.B.

PARKINSONISM, ITS MEDICAL AND SURGICAL THERAPY. By IRVING S. COOPER, M.D., PH.D., F.A.C.S., Professor of Research Surgery, New York University School of Medicine. Pp. 239; 250 ills. Springfield, Ill. Charles C Thomas, 1961. Price, $16.50.

The author states that the purpose of his monograph is to describe comprehensively the therapy of Parkinsonism and secondarily to summarize an investigation of the neurosurgical alleviation of this condition, which was initiated in 1952. He further states that since that date, 5000 Parkinsonian patients have been examined in considerable detail on his service, and nearly 1500 basal ganglion operations have been performed in selected patients.

The contents are divided into 8 chapters as follows:

Chapter 1) The Problem, Chapter 2) A Review of Surgical Approaches to the Treatment of Parkinsonism, Chapter 3) The Neuroanatomy, Neurophysiology, and Pathologic Physiology of the Globus Pallidus and Thalamus, Chapter 4) A Discussion of the Procedure of Surgical Occlusion of the Anterior Choroidal Artery: Results, Complications and Disadvantages of the Operation, Chapter 5) Chemopallidectomy and Chemothalmectomy: Basis for selection of patients, the basic principles of chemosurgery of the basal ganglia, anesthesia, surgical techniques, clinical results and complications of this procedure, Chapter 6) Roentgeno-anatomico-clinical correlations, Chapter 7) Case Histories, Chapter 8) Summary of the entire problem.

This handsome monograph does justice to the pioneer work of the author in the surgical treatment of Parkinsonism. It is well-organized, presents the known anatomic, physiologic and pathologic data and reviews the operations developed by other surgeons for this problem. The author gives in detail, and with excellent illustrations, the surgical technique of his methods of chemopallidectomy and chemothalmectomy. He presents statistical results of 1500 consecutive operations, and more than 50 case histories.

This monograph although primarily of value to the internist, neurologist, and neurosurgeon is also revealing to any interested in the development of surgical therapy for this most disabling condition.

Finally, the book is a fitting tribute to the persistence of Dr. Cooper and his associates in developing his procedure in a scientific manner against much resistance and criticism in the early years. His operation along with the stereotaxic methods first developed by Spiegel and Wycis are the accepted procedures for the surgical treatment of tremor and rigidity due to Parkinsonism. M.S.

THE NERVOUS SYSTEM: AN OUTLINE OF THE STRUCTURE AND FUNCTION OF THE HUMAN NERVOUS SYSTEM AND SENSE ORGANS. By G. M. WYBURN, University of Glasgow. Pp. 184; 108 ills. London: Academic Press, Inc., 1960. Price, $5.00.

THE author intended this book to be used in the ancillary facets of medicine. The typically British style (colour, sixpence, etc.) is fairly readable, but the presentation possesses some inadequacies attendant, no doubt,

upon the sententiousness of the contents, as for example, ". . . an oval swelling, the spinal ganglion," without stating the presence of cell bodies; or the use of vague terms, namely, "below and above" when caudal and rostral were meant in one instance, ventral and dorsal in another. Nerve pathways could be traced with greater clarity than that given in Chapter 4. Labels for the dorsal and ventral cochlear nuclei were reversed in Fig. 78.

Material presented out of context might engender misleading associations; for example, in the section under "Babinsky's sign," one short sentence only pertains to this diagnostic test, the remainder treats of the visceral reflex activity of the spinal cord.

The impression is gained that organization in this book embodies neither the precise descriptive or pictorial clarity of expression, nor the smooth flowing continuity of concepts required of an introductory text on the nervous system.

Excellent printing on off-white, pale buff colored stock can be read easily. Numerous figures, exclusively black line drawings, are generally clear; more would be helpful; some are too small. References, none of which the author dignified by citing, are conveniently placed at the ends of the chapters.

This book is not an outline; it is one that can be easily missed by students in medically related disciplines; it would not be of interest to medical students or graduate physicians.

J.B.

DEVELOPMENTAL GENETICS AND LETHAL FACTORS. By ERNST HADORN, Professor of Zoology and Comparative Anatomy, University of Zurich. Translated by URSULA MITTWOCH, Assistant Lecturer in Eugenics, University College, London. Pp. 355; 129 ills. London: Methuen & Co., Ltd. New York: John Wiley & Sons, Inc. 1961. Price, $8.50.

THIS book first appeared in German in 1955 as *Letalfaktoren in ihrer Bedeutung fur Erbpathologie und Genphysiologie der Entwicklung*. For the present English translation, which has been expertly executed, the book was slightly modified by the addition of about 100 recent references.

The main core of the book is Drosophila genetics, as would be expected. However, good balance in content is achieved by adequate coverage of lethal, semilethal and subvital factors in plants, bacteria and many animals including man. Repetition is at a minimum which points out the good organization of the text.

One of the better chapters "Phenocopies" aptly recalls that all that appears as the effect of genetic control may not be so; environmental factors may be responsible for phenotypic expression mimicking another genotype.

The book is an advanced text and should be of value to medical geneticists as well as to students in advanced zoology, biology or eugenics. The last 50 pages contain a glossary of terms, bibliography, author index and index. All illustrations, regardless of source, have been reproduced as good drawings. The printing is remarkably free of errors. The price seem reasonable.

K.S.

HYPOTHERMIA AND THE EFFECTS OF COLD. (Brit. Med. Bull., **17**, No. 1, January, 1961). Pp. 78; illustrated. London: Medical Department, British Council, 1961. Price, $3.25.

THE study of hypothermia in man and its possible clinical applications have received increasing attention since the pioneer efforts of Temple Fay and G. W. Smith just before World War II. A contemporary summary of progress in both the clinical and physiological aspects of hypothermia is provided in this issue. Surgeons, physiologists, biologists, aerospace scientists and others concerned with this important subject will find this an invaluable reference.

C.Z.

KLINIK UND THERAPIE DER PILZKRANKHEITEN. Edited by PRIV.-DOZ. DR. G. POLEMANN, Köln. Pp. 396; 142 ills. Stuttgart: Georg Thieme Verlag, 1961 (Intercontinental Medical Book Corp., New York, U.S. Agents). Price, $15.95.

RECENT additions to the therapy of fungal diseases have been responsible for intense, renewed interest in these processes. Accordingly a new, and, in this case, unique, presentation on mycology deserves critical evaluation. This book is the result of the collaboration of a dermatologist, an internist and a neurologist. The material is presented under the following heads: General mycology; European fungal infections of the skin; extra-European fungal infections of the skin; fungal infections of internal organs, and fungal diseases of the nervous system. The text is indexed as to authors and subjects. The illustrations are of good quality. As part of the general discussion, there is a glossary of terms used in mycology. On the whole the physical character of the volume is elegant and pleasant to handle. Therapy is up-to-date and contains relatively extensive discussion of the newer modes of systemic treatment. However,

there are a number of limitations to the value of the book, particularly for American readers: It is written in German; there is little illustration of the pathologic changes in the skin (there are some of the visceral lesions); there is lack of illustration of certain unusual diseases (for example, rhinosporidiosis) and the natural emphasis is on European mycology. H.B.

Medical Forms and Procedures for Industry. By Herbert L. Herschensohn, M.D., Associate Clinical Professor of Industrial Medicine and Associate Clinical Professor of Preventive Medicine and Public Health, University of California at Los Angeles. Pp. 192; 66 ills. Springfield: Charles C Thomas, 1961. Price, $8.50.

The author's thirty years of experience in industrial medicine is reflected in his succinct description of various medical problems in industry and his advice in guidance to a solution of those problems. The book is not divided in the conventional manner of chapter following chapter but rather topic after topic arranged alphabetically. The various topics considered are numerous and deal with many of the tacky situations arising in industry today. The author gives advice in the resolution of these problems and includes suggested medical forms appropriate to the situation. The book impresses me as a valuable one for the industrial physician's library as a ready reference in helping him solve new problems or aiding him in revising his former methods where indicated. J.M.

Epidemiology and Control of Communicable Diseases. By Fred B. Rogers, M.D., Temple University School of Medicine. Pp. 75; 1 ill., Baltimore: Waverly Press, Inc., 1961. Price, $5.00.

Dr. Fred B. Rogers is Professor of Preventive Medicine and is eminently qualified to discuss his subject. He has exhibited rare courage in publishing a syllabus of his lectures to medical students since at best, in such form, they must be greatly condensed or in outline. He has been able to compress a vast amount of information in small space although the book can serve only as a guide to further study of a vast subject. It suffers somewhat through inconsistencies in organization, for example, anthrax and tetanus under diseases transmitted via the intestinal tract and a long discussion of serum hepatitis under a subheading of infectious hepatitis in the same section. Diseases of viral etiology are discussed in several different sections and might better be drawn together and some of the less important ones eliminated.

All in all for the purposes for which it was written, it is an admirable "small book on a large topic" and should be of great value to the medical student or to one seeking to review the content of the subject expeditiously. T.W.

Progress in Endocrinology. Part II. Biochemistry and Biological Actions of Steroids and Other Hormones. Edited by K. Fotherby, J. A. Loraine, J. A. Strong, and P. Eckstein. No. 10. Pp. 167; 45 tables, 61 ills. New York: Cambridge University Press, 1961. Price, $8.50.

This excellent volume is a continuation of the previous number and contains further contributions from the Acta Endocrinologica Congresses held in Edinburgh, August, 1959. The various contributions by authorities, from the world over, cover the biochemistry and biological actions of steroid hormones. In addition, the relationship of endocrine glands to cancer, is considered in several chapters. Collectors of this series of Memoirs of the Society for Endocrinology, will find this number a most informative addition. A.B.

Biochemistry for Medical Students. By William V. Thorpe, M.A. (Cantab.), Ph.D. (Lond.), University of Birmingham, England. 7th ed. Pp. 552; 50 ills. London: J. & A. Churchill, Ltd., 1960 (Distributed in U.S. by Little, Brown & Co., Boston). Price, $9.00.

In this new edition the author attempts to modernize, especially in the chapters on enzymes, oxidation and reduction, metabolism and hormones, in the light of scientific developments since 1955. The author attempts rather successfully to steer a course between exhaustive and superficial presentation of the pertinent facts and concepts.

Clinical and physiologically relevant material is added at certain points for motivation and interest. This reviewer regrets omission of much material which might be considered "too clinical" for a first year medical student, but provides the aura of contact with practical medical problems which can serve to link the pre-clinical and clinical teaching into a better functioning whole.

The author has provided an appendix with useful conversion tables and an excellently selected bibliography (100 references). The index is an especially valuable part of the book and adds to its usability. J.B.

THE YEAR BOOK OF DRUG THERAPY (1960-1961 YEAR BOOK SERIES). Edited by HARRY BECKMAN, M.D., Chairman, Departments of Pharmacology, Marquette University Schools of Medicine and Dentistry. Pp. 587; 57 ills. Chicago: Year Book Publishers, Inc., 1961. Price, $8.50.

THIS volume, like its predecessors in this series, offers a critical evaluation of the new drugs which appeared in clinical publications during the year. The editor has again provided succinct but adequate abstracts of pertinent articles, and further enhanced their value to the reader in many instances by adding informative comments of his own.

Aside from its practical informational value, this volume is recommended also for the editor's very excellent introductory discussion, "Bases for Judgment of a New Drug."

C.Z.

THE HAND. By HENRY C. MARBLE, M.D., F.A.C.S., Consulting Surgeon, Massachusetts General Hospital. Pp. 197; 58 ills. Philadelphia: W. B. Saunders Co., 1961. Price, $7.00.

THIS short monograph has a subtitle, "A Manual and Atlas for the General Surgeon," which is an excellent summary of the book. The illustrations are very well done, all of them being simple line drawings in black and white. The text is well organized and presented in outline form with short explanatory descriptions where needed. This is complete and lucid treatment of hand surgery with easy reference and unusually good descriptive material. I feel that this book would be an asset to any general surgeon, to any surgical resident and would even be quite applicable for student teaching.

R.T.

A SYNOPSIS OF CONTEMPORARY PSYCHIATRY. By GEORGE A. ULETT, B.A., M.S., PH.D., M.D., Professor of Psychiatry, Washington University School of Medicine and D. WELLS GOODRICH, M.D., Chief, Biosocial Growth Center, National Institute of Mental Health. 2nd ed. Pp. 309. St. Louis: C. V. Mosby Company, 1960. Price, $6.50.

THIS handbook offers a clear presentation of major clinical psychiatric facts that the general practitioner and medical student will most commonly need in his work with patients. The book, written with exceptional clarity and lucidity, offers an amazingly extensive survey of the psychiatric field. There are 29 chapters, each followed by a list of suggested readings and a comprehensive index is included.

The chapter, Chemotherapy in Mental Illness, includes a tabular listing of all psychotropic drugs. It reviews the essential facts of most drugs that might be used in the treatment of psychiatric patients.

This synopsis should be welcomed by all persons becoming introduced into the field of psychiatry.

M.B.

CARCINOGENESIS. By I. HIEGER, Chester Beatty Research Institute, Royal Cancer Hospital, London. Pp. 138; 7 ills. London and New York: Academic Press, 1961. Price, $5.00.

To the author of this short book, carcinogenesis is the most important aspect of cancer research. He attempts to evaluate the many theories concerning carcinogenesis in the light of the knowledge which existed at the time a theory was proposed and that which exists today.

The reader finds that what he expects to be a scholarly work on the subject promptly becomes an arena of conflict. With hypercritical comments, some bordering on sarcasm, and with some accusations of naivete, omission, misinterpretation, and little research background the author tears apart the theories of Oberling, L. C. Strong, Darlington, H. N. Green, Rhoads and Kensler, Badger, Berenblum and Warburg. His criticism of the ideas of Burnet and Rous is somewhat apologetic. Boveri, Darlington, Fieser and Burnet are charged with using tautology.

One gains the impression that the author is the sole person qualified to advance a sound concept of carcinogenesis, yet none is advanced. It is unusual that the author, assessing the ideas of others, does not always know the sex of the person whose ideas he is appraising.

The book purposely has many lengthy direct quotations from other sources; this along with the style of the author does not make for a well-written book. It contains little new information and would seem to be of little value to the research worker.

K.S.

EINFÜHRUNG IN DIE BLUTMORPHOLOGIE. By DR. MED. D. SCHREIBER. Oberarzt der Medizinischen Klinik der Medizinischen Akademie Erfurt. Pp. 69; 27 color ills. Leipzig: Georg Thieme Verlag, 1960. Price, DM 17.30

FOR the physician or technician who occasionally sees abnormal cells, an atlas of hematology is an invaluable assistant al-

though the single picture as presented in illustrations as seen in an atlas is often difficult to correlate with what one sees under the microscope. Schreiber has attempted to give a simplified picture of what one might see in various hematological abnormalities both in the bone marrow and in the peripheral blood. He has placed his emphasis on the "general" picture seen by study of slides and less upon individual cell types, namely, "The interpretation of the single cell, however, is only the beginning of the assessment of a marrow smear. The final aim is always an understanding of the total picture of the marrow structure." Published in 3 languages (German, Russian and English) are short, concise descriptions of all the illustrations; some of the terminology might differ from that generally used in this country and might be confusing to the uninitiated. On the whole, the author has accomplished his purpose of publishing a simple, yet useful, atlas.

J.D.

CONGENITAL MALFORMATIONS OF THE HEART. VOLUME I. GENERAL CONSIDERATIONS. BY HELEN B. TAUSSIG, M.D., Professor of Pediatrics, Johns Hopkins University School of Medicine. Pp. 204; 56 ills. Cambridge, Massachusetts: Harvard University Press for the Commonwealth Fund, 1960. Price, $4.75.

DR. TAUSSIG has divided this second edition of her book into two volumes. Volume I alone is reviewed at this time. This deals with general considerations, leaving the specific cardiac entities to be discussed in Volume II.

Volume I is devoted to five chapters—1) Embryology and the analysis of the fetal circulation, 2) Methods of clinical diagnosis, 3) Special diagnostic procedures, 4) A consideration of cyanotic problems, 5) Medical care for the patient with congenital heart disease.

The high standard of the first edition has been maintained in Volume I of this edition. The illustrations should be especially helpful to the diagnostician in regard to interpretation of fluoroscopy and roentgenograms of the chest and also the interpretation of angiocardiograms. Intracardiac phonocardiography may not have been given as much attention as it deserves. The one most valuable diagnostic modality which is not discussed is the use of dye curves obtained at the time of cardiac catheterization. J.J.

WHO Chronicle, Vol. 15, No. 5–6, May–June, 1961. Pp. 76; 4 ills. Geneva: World Health Organization, 1961.

World Directory of Venereal-Disease Treatment Centres at Ports. 2nd ed. Pp. 164. Geneva: World Health Organization, 1961. Price, $1.75.

Praxis. Special edition issued on occasion of the fiftieth anniversary of the first appearance of this publication. Pp. 73; illustrated. Bern: Schweizerische Rundschau für Medizin Revue Suisse de Médecine, 23 March 1961.

European Standards for Drinking-Water. Pp. 52. Geneva: World Health Organization, 1961. Price, $.60.

Chronic Cor Pulmonale. Report of an Expert Committee. WHO Technical Report Series No. 213. Pp. 35. Geneva: World Health Organization, 1961. Price, $.30.

Molluscicides. Second Report of the Expert Committee on Bilharziasis. WHO Technical Report Series No. 214. Pp. 50; 1 ill. Geneva: World Health Organization, 1961. Price, $.60.

Planning of Public Health Services. Fourth Report of the Expert Committee on Public Health Administration. WHO Technical Report Series No. 215. Pp. 48. Geneva: World Health Organization, 1961. Price, $.60.

Expert Committee on Health Statistics. Seventh Report. WHO Technical Report Series No. 218. Pp. 28. Geneva: World Health Organization, 1961. Price, $.30.

International Work in Health Statistics, 1948–1958. BY H. S. GEAR, M.D., Y. BIRAUD, M.D., and S. SWAROOP, PH.D., M.P.H. Pp. 56. Geneva: World Health Organization, 1961. Price, $.60.

Genetic Perspectives in Disease Resistance and Susceptibility. BY HENRY A. WALLACE AND 16 OTHERS. (Ann. New York Acad. Sci., Vol. 91, Art. 3). Pp. 223; illustrated. New York: New York Academy of Sciences, 1961.

Automatic Process Monitoring. BY SIDNEY SIGGIA AND 10 OTHERS. (Ann. New York Acad. Sci., Vol. 91, Art. 4). Pp. 116; illustrated. New York: New York Academy of Sciences, 1961.

Vitamin C. By J. J. Burns and C. G. King and 53 others. Ann. New York Acad. Sci., Vol. 92, Art. 1. Pp. 332; illustrated. New York: New York Academy of Sciences, 1961.

Recommended Requirements for Schools of Public Health. Tenth Report of the Expert Committee on Professional and Technical Education of Medical and Auxiliary Personnel. WHO Technical Report Series No. 216. Pp. 24. Geneva: World Health Organization, 1961. Price, $.30.

Russian Drug Index. Compiled by Stanley Jablonski. Revised by Robert M. Leonard, Ph.D., Assistant Dean, George Washington University School of Pharmacy. Washington: U.S. Department of Health, Education, and Welfare, U.S. Public Health Service, 1961. Price, $.60.

As pointed out in the Preface, Russian drug names have often no relation to the generally accepted names for the same chemical agents in use in other parts of the world. This Index of Russian Drugs is, therefore, a valuable and important contribution in providing convenient and reliable access to Russian material.

World Health Organization Chronicle, Vol. 15, No. 4, April, 1961. Pp. 42; 7 ills. Geneva: World Health Organization, 1961. Price, $.30.

From Girlhood to Womanhood. By Albert Sharman, M.D., D.Sc., F.R.C.O.G. Pp. 72; 4 ills. Edinburgh and London: E. & S. Livingstone Ltd., 1960 (The Williams & Wilkins Company, Baltimore, U.S. Agents). Price, $1.75.

From *Girlhood to Womanhood*, which was ". . . designed mainly for the mother of the female teenager," contains a mass of information which includes the essentials of female anatomy and physiology, sexual activities, normal and abnormal pregnancy, fetal growth, development and physiology, labor, delivery, analgesia and sterility. It is more a compilation of physiologic facts than a manual from which a mother can obtain advice or reassurance concerning problems relating to a maturing daughter.

J.W.

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